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# Aldrichimica ACTA

VOL. 38, NO. 1 • 2005

## ROM Polymerization in Facilitated Synthesis

## Polyurea-Encapsulated Palladium Catalysts

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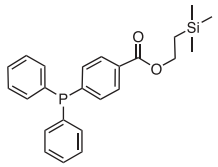
## 4-Diphenylphosphanylbenzoic acid, 2-(trimethylsilyl)ethyl ester, 0.5 M in THF

**63,801-3** — 5 mL, 25 mL

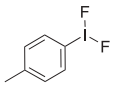


This reagent was developed to replace triphenylphosphine in the Mitsunobu reaction. The resulting phosphine oxide is easily removed from the reaction during workup.

Yoakim, C. et al. *Synlett* **2003**, 473.

## 4-Iodotoluene difluoride

**65,111-7** — 1 g, 5 g

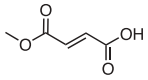


A new and efficient fluorinating reagent that is recommended for the fluorination of the α carbon of sulfanyl amides under mild conditions.

Motherwell, W. B. et al. *J. Chem. Soc., Perkin Trans. 1* **2002,** 2816.

## mono-Methyl fumarate, 97%

**65,141-9** — 1 g, 10 g

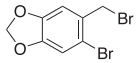


Employed in the design of affinity labels for opioid receptors[1] and in a highly stereoselective synthesis of optically active furfuryl fumarates.[2]

(1) Chang, A.-C. et al. *J. Med. Chem.* **1994**, *37,* 4490. (2) Butz, T.; Sauer, J. *Tetrahedron: Asymmetry* **1997**, *8,* 703.

## 5-Bromo-6-bromomethylbenzo[1,3]dioxole

**65,374-8** — 5 g, 25 g

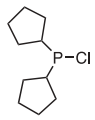


Has been utilized in the preparation of toddaquinoline, an unusual medicinal alkaloid,[1] and lignans, which are known for their biological activity and effectiveness as antineoplastic agents.[2]

(1) Harrowven, D. C. et al. *Tetrahedron* **2001**, *57,* 4447. (2) Cochran, J. E.; Padwa, A. *J. Org. Chem.* **1995**, *60,* 3938.

## Chlorodicyclopentylphosphine

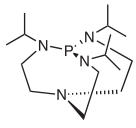
**64,906-6** — 1 g, 5 g, 25 g



A phosphine precursor for ligand preparation in Negishi and Suzuki coupling reactions.

## 2,8,9-Triisopropyl-2,5,8,9-tetraaza-1-phosphabicyclo[3,3,3]undecane, 1 M in toluene

**65,435-3** — 10 mL

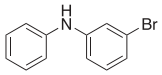


This highly useful and air-senstive reagent is now available in an easier-to-handle toluene solution in Sure/Seal™ bottles.

Verkade, J. G.; Kisanga, P. B. *Aldrichimica Acta* **2004**, *37,* 3.

## *N*-(3-Bromophenyl)aniline, 97%

**65,424-8** — 1 g, 10 g

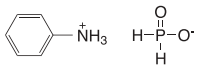


A useful building block in the preparation of triarylamines, which have been extensively employed in electroluminescent materials as hole-transport materials and hole-transport emitters,[1] and in the development of organic-based magnets.[2,3]

(1) Mitschke, U.; Bäuerle, P. *J. Mater. Chem.* **2000**, *10,* 1471. (2) Miller, J. S.; Epstein, A. J. *MRS Bull.* **2000**, *25,* 21. (3) Veciana, J.; Iwamura, H. *MRS Bull.* **2000**, *25,* 41.

## Anilinium hypophosphite

**65,411-6** — 25 g

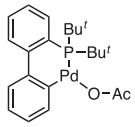


An easy-to-handle and relatively nonhygroscopic reagent that has been used in the preparation of monosubstituted phosphinic acids via Pd-catalyzed reaction with aryl halides or triflates.[1] A practical triethylborane-initiated radical addition of anilinium hypophosphite to olefins has been reported.[2]

(1) Montchamp, J.-L.; Dumond, Y. R. *J. Am. Chem. Soc.* **2001**, *123,* 510. (2) Deprele, S.; Montchamp, J.-L. *J. Org. Chem.* **2001**, *66,* 6745.

## 2-(2′-Di-*tert*-butylphosphine)biphenylpalladium(II) acetate

**65,541-4** — 250 mg, 1 g

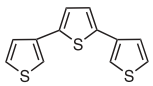


A novel, air- and moisture-stable pre-catalyst for the amination of aryl chlorides.

Zim, D.; Buchwald, S. L. *Org. Lett.* **2003**, *5,* 2413.

## 3,2′:5′,3″-Terthiophene

**65,138-9** — 1 g

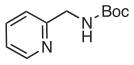


An efficient singlet-oxygen sensitizer. This compound is also associated with photoantibiotic and phototoxic properties.[1,2]

(1) Beny, J.-P. et al. *J. Org. Chem.* **1982**, *47,* 2201. (2) Moriarty, R. M. et al. *Synth. Commun.* **1985**, *15,* 789.

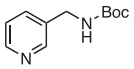
## *N*-Boc-2-aminomethylpyridine, 97%

**65,157-5** — 5 g, 25 g



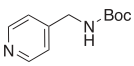
## *N*-Boc-3-aminomethylpyridine, 97%

**63,444-1** — 1 g, 5 g



## *N*-Boc-4-aminomethylpyridine, 96%

**64,976-7** — 1 g, 10 g



These Boc-protected pyridines can be used as pharmaceutical building blocks in thrombin[1] and PKC inhibitor[2] research, and can be readily hydrogenated to the protected piperidines.

(1) Hilpert, K. et al. *J. Med. Chem.* **1994**, *37,* 3889. (2) Shearer, B. G. et al. *J. Med. Chem.* **1991**, *34,* 2928.

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Professor Ei-ichi Negishi of Purdue University kindly suggested that we offer *trans*-1-bromo-2-iodoethene, a useful synthon in Pd-catalyzed cross-coupling reactions. Its utility has recently been demonstrated in the synthesis of xerulin, an inhibitor of cholesterol biosynthesis,[1] *cis*- and *trans*-bupleurynol,[2] in the preparation of 1-halo-1,3-dienes,[3] and in coupling reactions with alkynylzinc reagents.[4]

(1) Negishi, E.; Alimardanov, A.; Xu, C. *Org. Lett.* **2000**, *2*, 65. (2) Ghasemi, H.; Antunes, L. M.; Organ, M. G. *Org. Lett.* **2004**, *6*, 2913. (3) Qian, M.; Huang, Z.; Negishi, E. *Org. Lett.* **2004**, *6*, 1531. (4) Negishi, E.; Qian, M.; Zeng, F.; Anastasia, L.; Babinski, D. *Org. Lett.* **2003**, *5*, 1597.


**57,780-4** ***trans*-1-Bromo-2-iodoethene, 97%** 5 g, 25 g

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

*The Fence* (oil on canvas, 37.8 × 45.7 cm) was signed and dated by the French painter Camille Jacob Pissarro in 1872. During the 1860s, Pissarro moved his family from Paris to various small villages in the French countryside. He was committed to the principles of socialism, and felt a strong affinity for the peasant farmers who worked the land. Like the other impressionists, Pissarro chose to represent subjects from modern life; but, while they often painted the pleasures of the urban bourgeoisie, scenes from the theatre, the opera, the ballet, or the racetrack, Pissarro was more likely to portray the rustic life of farmers working in the fields with whom he identified.

The warm colors of the trees and shrubbery in the picture show that it is the fall of the year. At the left in the foreground is a large bent and broken tree, whose almost leafless branches are silhouetted against the light sky. Near the lower right corner of the painting, a peasant couple chat together on either side of a rustic fence. In the distance, one can make out the buildings of the local village, towards which a woman moves along the path near the right edge of the picture. As in a snapshot, nothing in nature has been rearranged to create a more pleasing, harmonious, or picturesque effect. The rapidly executed brushwork is variegated to suggest the different textures of diverse objects in the painting, which was almost certainly painted in a single session on the site. One might say, in fact, that a central purpose of all the impressionist artists was not to create an invented world on canvas, but to capture the immediacy of the unique conditions of a specific moment in time in a particular place.

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

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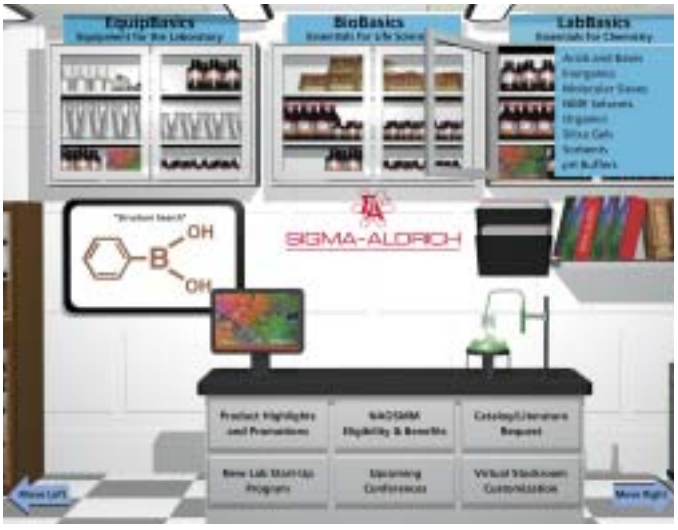


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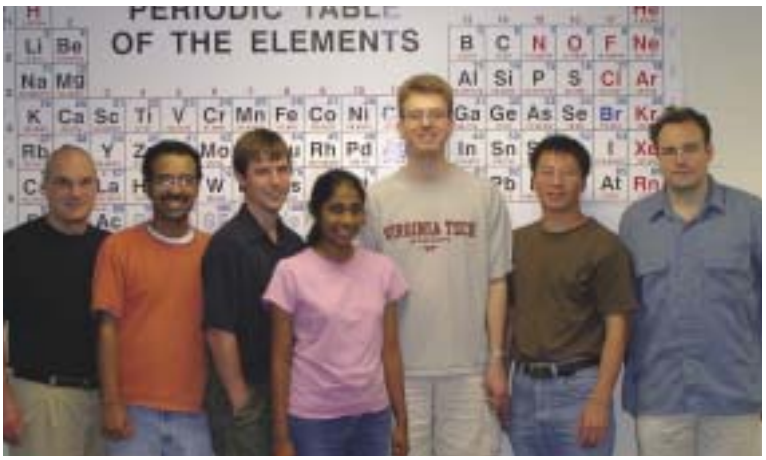
# ROM Polymerization in Facilitated Synthesis




From left to right: D. L. Flynn, S. Mukherjee, R. H. Herpel, P. Vedantham, A. M. Harned, M. Zhang, and P. R. Hanson.

*Andrew M. Harned,[§,¥] Mianji Zhang,[§,¥] Punitha Vedantham,[§,¥] Shubhasish Mukherjee,[§,¥] Russell H. Herpel,[§,¥] Daniel L. Flynn,[*,§,£] and Paul R. Hanson[*,§,¥,†]*

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## Outline



## 1. Introduction

The recent growth of high-throughput screening for biologically active agents has increased the demand for the rapid production of chemical compounds. In this context, an array of polymer-bound reagents and scavengers have been reported.[1] These effectively eliminate or circumvent the need for chromatographic purifications, which typically is a bottleneck in synthetic sequences. Recent successes in multistep total syntheses—exclusively using immobilized reagents and scavengers, whereby filtration was the sole purification protocol—are a testament to the power of this approach.[2] Despite tremendous advances in this area, *limitations in nonlinear reaction kinetics, low resin-load capacities, and the means of distributing reagents* continue to warrant the development of designer polymers.

In order to address these limitations, soluble polymers[3] and scavenger resins[1] have emerged as a means of utilizing solution-phase reaction kinetics with all the advantages of their solid-phase counterparts. Pioneering work by Barrett[4] and others[5,6] has led to the general use of ring-opening metathesis polymerization (ROMP) for the generation of high-load, immobilized reagents, while advances in ROM polymer-immobilized catalysts were simultaneously championed by Buchmeiser[7] and Bolm.[8] Overall, the ability to produce designer, ROMP-derived polymers with tunable properties has become a powerful technological advancement in the arena of facilitated synthesis. Related reviews have appeared that cover advances in this field through 2002.[4,5,6]

This review will report on more recent advances in the use of ROM polymerization for facilitated synthesis.

## 2. ROM Polymerization

Ring-opening metathesis polymerization (ROMP) has a history that harks back to the late 1950s and early 1960s.[9] Since then, it has remained in the realm of classical polymer chemistry. This, in part, can be attributed to the lack of robust, well-defined catalysts to initiate the polymerization. Some of the early initiator systems used were $MoCl_5$–$Et_3Al$, $WCl_6$–$Et_3Al$, various Ti-based systems and, later, $RuCl_3$. With the development of the highly active molybdenum imido alkylidene complexes (cat-**C**, **Figure 1**) by Schrock in the late 1980s,[10,11] the first well-defined ROM polymerizations could be accomplished in a controlled manner. Although these complexes are not water- and oxygen-tolerant, they do show a higher tolerance of Lewis basic moieties when compared to the earlier initiators. In the mid-1990s, Grubbs and co-workers introduced the highly functional group tolerant ruthenium alkylidene complexes (cat-**A** and cat-**D**, **Figure 1**).[12] This was followed by an explosion of development in ROMP and ring-closing olefin metathesis (RCM). Concurrently, a number of newer and more active Ru-based catalysts (cat-**B**, cat-**E**, and cat-**F**) have emerged that rival and, at times, surpass the activity of the Schrock systems.

## 3. Mechanism of ROMP

Grubbs and co-workers have performed a number of kinetic studies with $(PCy_3)_2(Cl)_2Ru{=}CHPh$ (cat-**A**)[13] and $(ImMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ (cat-**B**)[14], and a detailed mechanistic picture is beginning to emerge (**Scheme 1**).[15] The first step of this process involves dissociation of a phosphine ligand from the precatalyst, **1**. The resulting 14-electron complex, **2**, undergoes a [2+2] cycloaddition with monomer **3** to give metallacyclobutane intermediate **4**, which rapidly undergoes a [2+2] cycloreversion to produce ring-opened product **5**. This sequence is highly favored due to the relief of ring strain of the initial monomer species. Intermediate **5** contains a catalytically active Ru-alkylidene, and undergoes further reactions until monomer **3** is completely consumed. The Ru center remains attached to oligomer **6** until the polymerization is quenched by the addition of ethyl vinyl ether (EVE). This quench results in polymer **8** and alkoxycarbene complex **7**. The length of oligomer **8** is conveniently controlled through the amount of catalyst employed for the polymerization; more catalyst will produce shorter oligomers, while less catalyst will produce longer oligomers. Because the initiation rate is similar to the propagation rate, 10 mol % of catalyst (10:1 monomer: catalyst) will produce mainly 10-mers, 5 mol % of catalyst (20:1 monomer:catalyst) will produce mainly 20-mers, etc.

As a polymerization technique, ROM polymerization is selective for strained, cyclic olefins. Typically, the monomers used are norbornene- or 7-oxanorbornene-based. As such, they can easily be prepared from a Diels–Alder reaction between cyclopentadiene or furan with a suitable dienophile, or from Pd-catalyzed reactions involving norbornadiene. Because of the low cost and ready availability of these starting materials, monomers can be constructed on a large scale. ROMP is also a very "organic chemist friendly" polymerization technique. The catalysts are commercially available and are no different than those used to perform the familiar RCM reaction. The only difference is that ROM polymerizations are typically performed at higher substrate concentrations (0.1 M) than RCM (0.01–0.005 M). In addition, no special equipment is required to perform ROM polymerizations. A polymerization can be carried out in flasks or screw-cap vials, inside or outside of a glove box. Reaction scale is not an issue, as polymerizations can be conducted on scales ranging from 10–20 milligrams up to kilograms.

There are a few other relevant characteristics of ROMP that should be addressed. First, the length of the ROM polymer can have a profound effect on its solubility. Typically, shorter oligomers will remain soluble in common reaction solvents ($CH_2Cl_2$, $CHCl_3$, THF, DMF), yet can often be precipitated from MeOH, $Et_2O$, EtOAc, or hexanes. It is also possible to control the solubility of the ROM polymers through the judicious use of cross-linking agents (**CL-1**, **CL-2**, and **CL-3**, **Figure 2**). ROM polymers constructed using cross-linkers typically result in insoluble gels, which retain swelling properties that are analogous to those of traditional solid-phase resins.[4]

Overall, polymers derived from ROM polymerization possess unique physical properties that depend largely upon the collective properties of the polymer backbone (*i.e., norbornene-based scaffold*), the individual functional groups (FG) that are placed on each monomer, the amount and nature of the catalyst used during the polymerization, and any cross-linker that may be added. It is these collective properties that have been the hallmark of ROM polymerization in producing designer polymers for facilitated synthesis.

## 4. ROMP-Derived Reagents and Scavengers

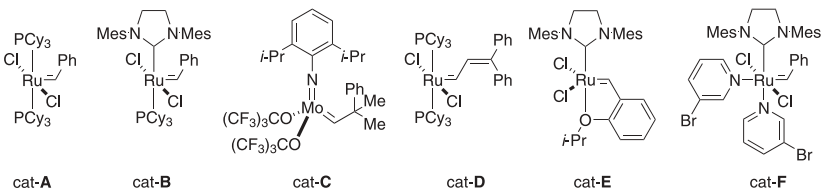
### *4.1. Barrett's ROMPgel Reagents and Scavengers*

The emergence of ROM polymerization in combinatorial chemistry was led by Barrett and co-workers, who developed a number of ROMP-derived reagents and scavengers, **9–19**, termed ROMPgels and a ROMPsphere (**Figure 3**).[4,16–23] Most of the reagents incorporated norbornenyl-derived cross-linkers to enhance swelling properties and ensure insolubility. Occasionally, the polymer backbone was hydrogenated under high pressure, as in **16** and **17**, using Wilkinson's catalyst. Barrett's seminal 2002 review[4] discusses a wide variety of ROMPgel-supported reagents (e.g., Horner–Wadsworth–Emmons reagent **9**;[16] amine- and hydrazine-scavenging agent **10**;[17] amine base **11**;[17] *N*-hydroxysuccinimide reagents **12**[18] and **13**[19], used for various acylations[18] and Mosher amide formation;[19] 4-toluenesulfonylmethyl isocyanide (Tosmic reagent) **14**;[20] allylboronate **15**;[21] biphenyl reagent **16**;[22] naphthalene reagent **17**;[22] and triphenylphosphine reagent **18**[23]) and ROMPsphere-supported peptide-coupling reagent **19**.[4]

Since 2002, additional high-load ROMP-derived reagents have been developed and are described in detail below, including: (i) ROMPgel-supported ethyl 1-diazo-2-oxopropylphosphonate for the conversion of aldehydes into terminal alkynes,[24] (ii) oligomeric benzylating agents (OBA)[25] for the benzylation of amines, and (iii) oligomeric alkyl cyclohexyl carbodiimides (OACC) for coupling reactions.[26] In addition, a number of high-load, soluble and insoluble nucleophile scavengers have been prepared, including oligomeric sulfonyl chlorides (OSC),[27] bis(acid chlorides) (OBAC),[28a] and phosphonyl chlorides (OPC).[28b]

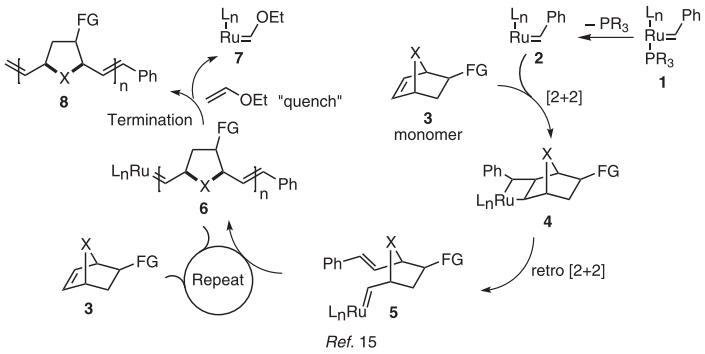
### *4.2. ROMPgel-Supported Ethyl 1-Diazo-2-oxopropylphosphonate for Seyferth–Gilbert Homologations*

The generation of alkynes using an immobilized reagent opens up new avenues for the rapid generation of chemical libraries due to the versatility of this functional group. Despite the potential utility of this chemical diversification step, only a single example existed in the literature prior to 2004,[29] when Barrett and co-workers reported the preparation of ROMPgel **25** (**Scheme 2**).[24]




Schrock's catalyst: cat-**C**; Grubbs' catalysts: cat-**A**, cat-**B**, cat-**D**, and cat-**F**; Hoveyda's catalyst: cat-**E**

**Figure 1.** Examples of the Most Widely Used Olefin-Metathesis Catalysts.




**Scheme 1.** Mechanism of ROMP.


**Figure 2.** Typical Cross-Linking Agents Used in ROM Polymerization.

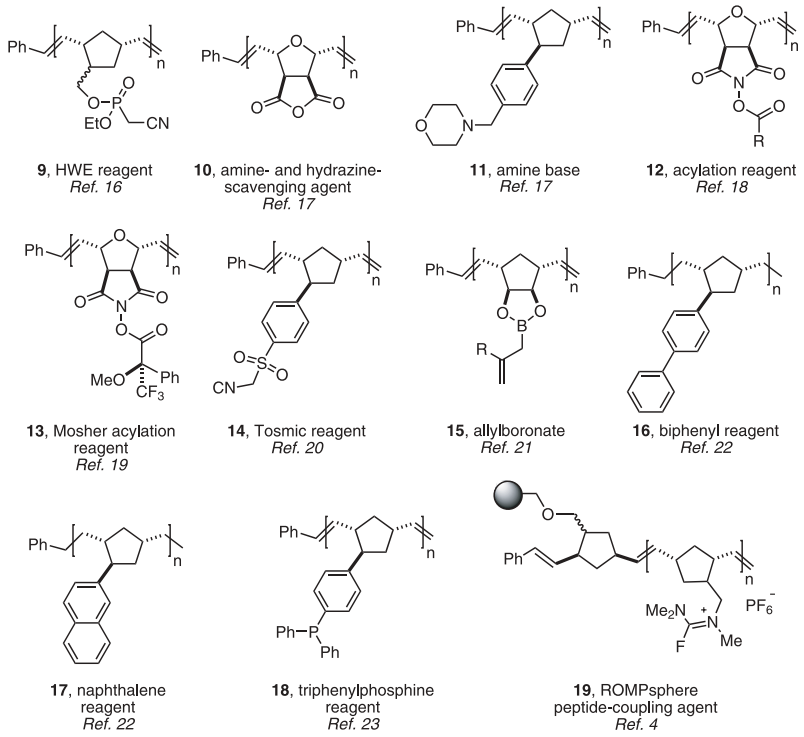
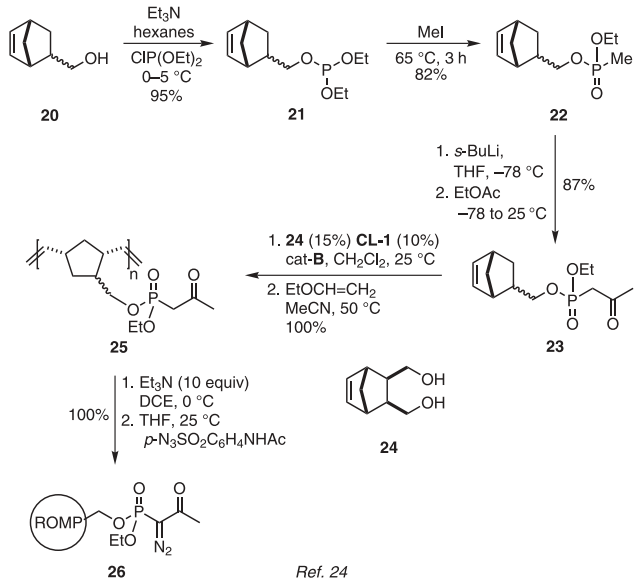
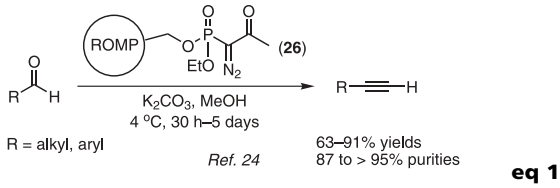



**Figure 3.** Barrett's ROMPgel (**9–18**) and ROMPsphere (**19**) Supported Reagents and Scavengers through 2002.

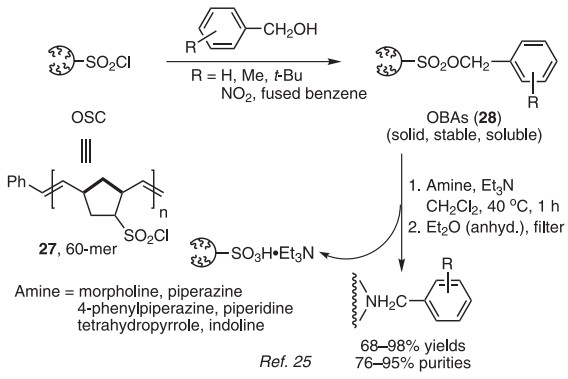
Bicyclo[2.2.1]hept-5-en-2-ylmethyl diethyl phosphite (**21**) was prepared by treating commercially available alcohol **20** with $ClP(OEt)_2$.[16] Reaction of phosphite **21** with $MeCOCH_2I$ gave the desired Michaelis–Arbuzov product **23** in variable yields (23–46%). Alternatively, phosphonate **23** was obtained in a higher overall yield by first reacting phosphite **21** with MeI to furnish phosphonate **22** (82%), followed by deprotonation of **22** with *sec*-butyllithium, and subsequent treatment with EtOAc (87%). After optimization, it was found that monomer **23** was readily polymerized in the presence of cross-linker **CL-1** (10 mol %) and co-monomer **24** (15 mol %), using cat-**B** to afford ROMPgel **25** in quantitative yield. This ROMPgel was found to have optimal swelling properties. The diazo functional group was quantitatively transferred to ROMPgel **25** under mild reaction conditions to produce ROMPgel **26** with a loading of 2.70 mmol/g. This route was found to be readily amenable to multigram-scale synthesis. Supported reagent **26** is stable at 0 °C, and retains its activity over a three-week storage period. Reaction of ROMPgel **26** with a variety of aldehydes generated the corresponding terminal alkynes in good yields and high purities (**eq 1**).[24]




**Scheme 2.** Synthesis of ROMPgel-Supported Ethyl 1-Diazo-2-oxopropylphosphonate (**26**).




**eq 1**




**Scheme 3.** Synthesis and Reactions of Oligomeric Benzylating Agents (OBA).

## 4.3. Oligomeric Benzylating Agents (OBA)

In 1996, Hunt and Roush developed immobilized alkylating agents.[30] Reitz and co-workers subsequently reported the use of a polystyrene resin bound sulfonyl chloride, which was "activated" with a variety of alcohols and further reacted in situ with a panel of amines to achieve the desired alkylation in a process termed "catch and release".[31] ROMP-derived oligomeric benzylating agents (OBA, **28**) were first reported in 2004 (**Scheme 3**).[25] These reagents were prepared from oligomeric sulfonyl chloride (OSC)[27] reagent **27** and various benzyl alcohols. They exist as free-flowing powders that dissolve readily in $CH_2Cl_2$ and are stable at refrigerated temperatures. Purification of the benzylation reaction products is accomplished by simple filtration, followed by solvent removal to deliver the desired benzylated products in good-to-excellent yields and high purities. These OBA entities have proven extremely efficient in the benzylation of cyclic, secondary amines and, with limited success, of acyclic amines. Furthermore, the solubility of OBAs enables convenient dispensing, which ultimately will provide an advantage in parallel-array synthetic protocols.

## 4.4. Oligomeric Alkyl Cyclohexyl Carbodiimides (OACC)

Carbodiimides rank as one of the most important classes of reagents in organic synthesis due to their accessibility and versatile chemical properties.[32] Complete removal of the dicyclohexyl urea (DCU) byproduct, when DCC is employed, usually necessitates additional purifications. This limitation has prompted the development of a class of soluble oligomeric reagents ($^{2G}OACC_n$),[26,33] which serve as viable alternatives to DCC.

The requisite monomer **32** was produced in three steps from commercially available *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (**29**) (**Scheme 4**).[26] Heating **29** at reflux with 1,2-diaminoethane (4 equiv) in toluene overnight gave mono-*endo*-amine **30**.[34] Treatment of **30** with cyclohexyl isocyanate produced the norbornenyl-tagged urea, **31**, in high yield. Dehydration of **31** with phenylsulfonyl chloride (2 equiv) in triethylamine (5 equiv) at 70 °C afforded the required monomer **32** in 73% yield. Subsequent ROM polymerization with $(H_2ImMes)(PCy_3)(Cl)_2Ru$=CHPh (cat-**B**) yielded oligomers **33** (n = 50, 100, 150) of the OACC reagent depending on the amount of cat-**B** used. Quenching of the ROM polymerization with EVE produced a free-flowing solid with a theoretical load of 3.2 mmol/g[35] and possessing a wide solubility profile: soluble in $CH_2Cl_2$, THF, DMF, and DMSO; and insoluble in $Et_2O$, EtOAc, and MeOH.

The oligomeric reagent $^{2G}OACC_{50}$ (**33**, Scheme 4) was initially developed as a coupling reagent for esterification, amidation, and dehydration of carboxylic acids (aliphatic and aromatic) with an assortment of alcohols (aliphatic 1°, 2°, and benzylic), thiols, phenols, and amines (aliphatic 1°, 2°, benzylic, and anilines). Following the coupling event, precipitation with an appropriate solvent ($Et_2O$, MeOH, or EtOAc), followed by filtration via solid-phase extraction (SPE) on silica gel provided the products in good-to-excellent yields and purities (**Scheme 5**).[26] Further studies determined that the longer oligomeric reagent $^{2G}OACC_{100}$

(**33**, Scheme 4), possesses the optimal length that provides facile precipitation during workup, while preserving the homogeneity of the reaction mixture.

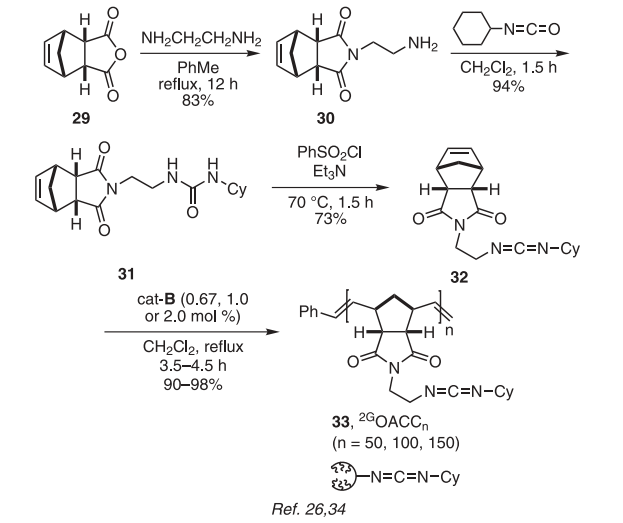
### 4.5. High-Load, Soluble Oligomeric Sulfonyl Chlorides (OSC)

The emergence of molecular scavenging[2] as a powerful purification technique has led to the development of a number of designer polymers, that are capable of discrete binding of excess reagent, in order to address limits in load and heterogeneity. In this regard, the aforementioned OSC reagent **27** was investigated as a high-load, soluble nucleophile scavenger (**Scheme 6**).[27] Simple preparation of **27** was achieved by the Diels–Alder reaction of vinylsulfonyl chloride (**34**) and cyclopentadiene to generate monomer **35** in 90% yield. ROM polymerization of **35** with cat-**B** produced **27** as a free-flowing solid. Arrays of polymers with different lengths (e.g., 10-mer, 30-mer, 60-mer, and 100-mer) were produced; the 60-mer ($^{2G}OSC_{60}$) proved to be the scavenging reagent of choice by virtue of its precipitation characteristics and differential solubility. $^{2G}OSC_{60}$ is soluble in $CH_2Cl_2$, THF, and DMF, but is insoluble in $Et_2O$, EtOAc, and MeOH.[36] The scavenging ability of $^{2G}OSC_{60}$ was investigated in the benzoylation and sulfonation of a variety of amines. Following the benzoylation or sulfonation reaction, $^{2G}OSC_{60}$ was added as a dichloromethane solution to remove the excess amine (1°, 2°, or benzylic), followed by precipitation of the scavenger to furnish the benzamides and sulfonamides in excellent yields and purities.[27]

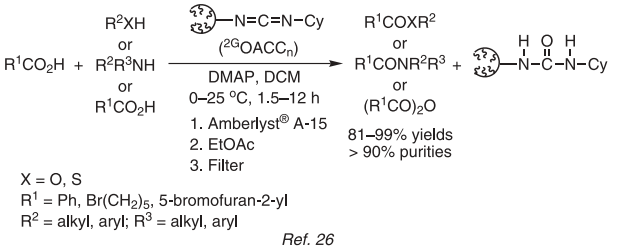
### 4.6. High-Load, Oligomeric Bis(acid chlorides) (OBAC)

In 2003, a high-load, oligomeric bis(acid chloride) (OBAC) was reported as a general nucleophile scavenger that was capable of removing alcohols and thiols in addition to amines.[28a] Like the aforementioned OSC scavenger, this system also offered flexible oligomer design and differential solubility for facile purification via simple precipitation–filtering protocols. The requisite monomer, *trans*-bicyclo[2.2.1]hept-5-ene-2,3-dicarbonyl dichloride (**37**), was conveniently prepared in two steps: a Diels–Alder reaction between fumaric acid and cyclopentadiene, followed by chlorination using oxalyl chloride and a catalytic amount of DMF (**Scheme 7**).[28a] Subsequent ROM polymerization with either 1 mol % cat-**B** or 2.5 mol % cat-**A** yielded the 100-mer (**38a**) or 40-mer (**38b**) OBAC reagents, respectively.[36] It is interesting to note that polymerization with 1 mol % of cat-**B** provided a heterogeneous, solid nucleophile scavenger ($^{2G}OBAC_{100}$), while polymerization with 2.5 mol % of catalyst cat-**A** yielded a homogeneous, soluble 40-mer ($^{1G}OBAC_{40}$).

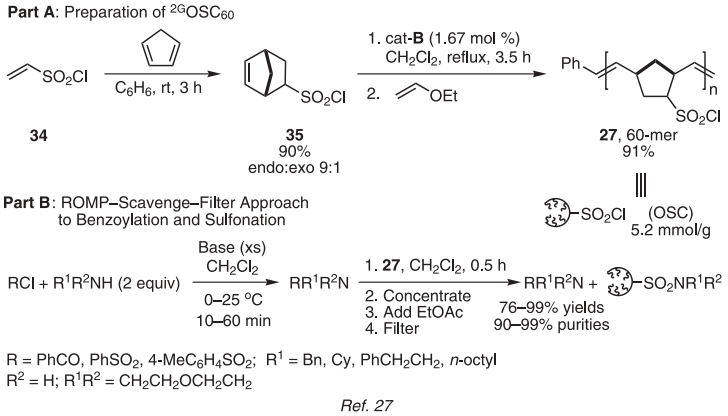
The scavenging ability of OBAC was tested with a variety of amines, alcohols, and thiols. OBAC was found to efficiently remove excess amines (1° and 2°), alcohols (1°, 2°, allylic, propargylic, and benzylic), and thiols after a common benzoylation event.[28a] While the amines were scavenged in 15–30 minutes at




**Scheme 4.** Synthesis of Oligomeric Alkyl Cyclohexyl Carbodiimides (OACC).

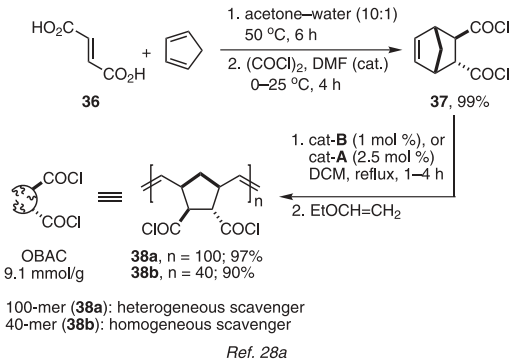



**Scheme 5.** Application of OACC Coupling Reagents.

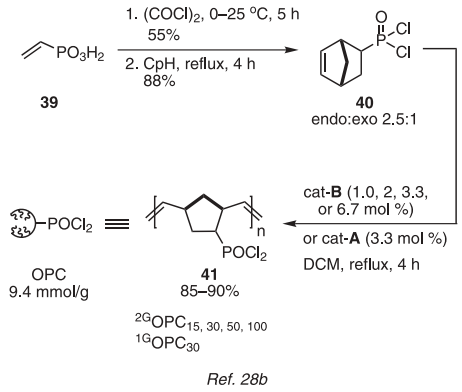



**Scheme 6.** High-Load $^{2G}OSC_{60}$ as a Nucleophile Scavenger.

room temperature, higher temperatures (refluxing DCM, 1–2 hours) were required for efficient scavenging of alcohols and thiols. The synthetic utility of OBAC scavengers was evaluated by comparing their efficiency against a commercially available nucleophile scavenger, polystyrene-based isocyanate (PS-NCO) resin.[1e,37,38] One clear advantage pertains to the loadings of OBAC scavengers, which are higher than the corresponding ones for the polystyrene isocyanate resin (theoretical load of 9.1 mmol/g vs ~1.3 mmol/g). Thus, the weight of OBAC reagent required for each scavenging reaction is seven times lower than the amount of isocyanate resin for a given experimental procedure. In a typical comparison experiment, 35 mg of OBAC versus 250 mg of the polystyrene-based isocyanate was found to be optimal for scavenging.[28a] While both OBAC and PS-NCO performed similarly for amines and thiols, OBAC was more efficient in scavenging alcohols.




**Scheme 7.** Preparation of High-Load, Oligomeric Bis(acid chlorides) (OBAC).




**Scheme 8.** Synthesis of Oligomeric Phosphonyl Chlorides (OPC).

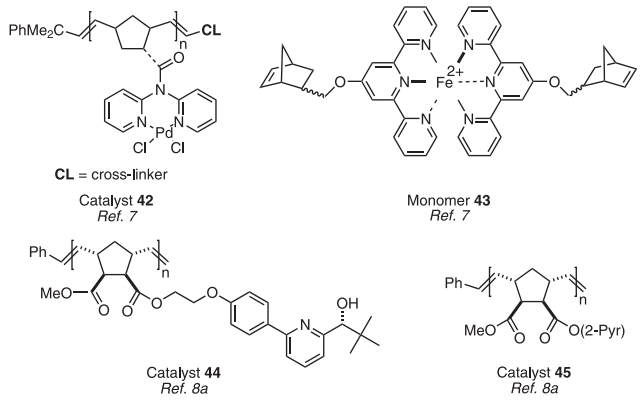



**Figure 4.** ROM Polymer-Supported Catalysts through 2002.

## 4.7. High-Load, Oligomeric Phosphonyl Chlorides (OPC)

A high-load, ROMP-derived phosphonyl chloride scavenging agent has also recently been realized. Chlorination of vinyl phosphonic acid (**39**), followed by [4+2] cycloaddition onto cyclopentadiene, furnished monomer **40** as a ~2.5:1 endo:exo mixture (**Scheme 8**).[28b] Subsequent ROM polymerization with cat-**A** or cat-**B** provided $^{1G}OPC_{30}$, $^{2G}OPC_{30}$, and $^{2G}OPC_{100}$, respectively (**41**). All OPCs efficiently removed both primary and secondary amines from reaction mixtures after benzoylation.

Overall, OSC, OBAC, and OPC scavengers have been conveniently prepared on a large scale from inexpensive and readily available starting materials. Furthermore, these scavenging reagents offer high-load benefits, exhibit wide solubility profiles, and have tunable properties that allow them to be isolated as either homogeneous or heterogeneous oligomers depending on the amount and nature of the catalyst used.

## 5. ROM Polymer-Supported Catalysts and Ligands

### 5.1. Buchmeiser's and Bolm's ROM Polymer-Immobilized Catalysts and Ligands

The use of ROM polymeric supports for immobilizing catalysts was pioneered by Buchmeiser[7] and Bolm[8] in the late 1990s, and much of this work has been reviewed.[4,6] Buchmeiser utilized ROM polymerization to generate an array of dipyridyl-based Pd(II) catalysts similar to catalyst **42** (**Figure 4**).[7] Dimeric iron complex **43** was also polymerized and used in heterogeneous atom-transfer radical polymerizations of styrene.[7] More recently, a grafted monolithic metathesis catalyst has been developed.[39] Concurrently, Bolm and co-workers developed the first soluble oligomeric chiral catalysts, **44** and **45**, for use in asymmetric diethylzinc addition reactions.[8a]

Since Barrett's review,[4] three additional ROM polymer-supported catalytic systems have been developed, including (i) a ROMPgel-supported tris(triphenylphosphine)rhodium(I) chloride for the hydrogenation of alkenes and terminal alkynes,[40] (ii) a bisphosphine oligomeric ligand used in supported, palladium-containing catalysts for the Heck, Sonogashira, and Negishi reactions,[41] and (iii) a ROMPgel-supported thiazolium iodide for use in Stetter reactions.[42a] Additionally, Tanyeli and Gümüş[42b] have developed ROMP-supported TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) catalysts for the oxidation of various primary alcohols to the corresponding aldehydes in 70–87% yields.

### 5.2. ROMPgel-Supported Tris(triphenylphosphine)rhodium(I)

Wilkinson's catalyst, $(Ph_3P)_3RhCl$, is widely used for the selective hydrogenation of sterically unhindered, nonconjugated alkenes.[43,44] Despite its advantages, Wilkinson's catalyst suffers from the need to separate the catalyst from the product. In 2003, Barrett's group prepared a novel ROM polymer-supported Wilkinson's catalyst. The monomeric ligands **48** and **52** were

synthesized in two or three steps from commercially available starting materials (**Scheme 9**).[40]

4-Bromoiodobenzene (**46**) was coupled to norbornadiene via a reductive Heck reaction to furnish aryl bromide **47**, which was allowed to react with BuLi and $Ph_2PCl$ to produce phosphine ligand **48**.[23] *N*-Alkylimidazole **50**[45] reacted with BnCl in toluene to give imidazolium chloride **51**, which underwent ion exchange with $KPF_6$ in $CH_2Cl_2$ to yield ligand **52**. ROM polymerization of **48**, **52**, and a 2:3 mixture of **48:52**, with cross-linker **CL-1** (10 mol %) and cat-**B**, generated oligomeric ligands **49**, **53**, and **54**, respectively.[40] Wilkinson's catalyst (**56**) was anchored to ROMPgels **49**, **53**, and **54** by heating a suspension of the polymer and the rhodium complex **55** or **56** in $CH_2Cl_2$ to give the ligand-displaced catalysts **57** and **58**, and the noncovalently bonded ionic catalyst **59** (**eq 2** and **3**).[40] ROMPgels **57** and **58** have been effectively utilized in the selective hydrogenation of a variety of alkenes and terminal alkynes. ROMPgel **57** turned out to be significantly more active than **58**, whereas ROMPgel **59** showed no activity in the hydrogenation reaction.[40]

### 5.3. Oligomeric Bisphosphine Ligand for Pd-Catalyzed C–C-Bond Formation

In 2003, Yang and Luh reported the preparation of bisphosphine polymer **64** (**Scheme 10**) by ROM polymerization of the corresponding monomer, **63**, and the use of **64** as a polymer-supported ligand in palladium-catalyzed, C–C-bond-forming reactions.[41] Treatment of **61** with $K_2CO_3$ and 4-bromobenzyl bromide in refluxing $CH_3CN$ afforded dibromide **62** in 78% yield. Reaction of **62** with *n*-BuLi at –78 °C, followed by displacement with $ClPPh_2$, gave monomer **63** in 60% yield. Polymerization of **63** using cat-**B** in THF (rt for 24 h) generated polymer **64** in powder form and 90% yield. Phosphine polymer **64** has a theoretical load of 2.8 mmol/g and, at room temperature, is soluble in moderately polar organic solvents such as THF, toluene, or dichloromethane; but is insoluble in alkanes, ether, and DMF. However, a homogeneous solution of **64** in DMF was obtained at an elevated temperature (80 °C).

A series of coupling reactions were examined to test the efficiency of polymeric ligand **64**. All Heck, Sonogashira, and Negishi reactions (**eq 4**, **5**, and **6**) proceeded smoothly to give high yields of the coupled products.[41] Furthermore, the catalysts retained most of their activities in subsequent cycles (4–5 cycles). When the small-molecule counterpart, 4-(methoxymethylphenyl) diphenylphosphine [$(4\text{-}MeOCH_2C_6H_4)Ph_2P$], was used as the ligand under identical conditions, no reactions were observed in the third cycle of the Heck and Sonogashira reactions and the second cycle of the Negishi reaction. This is presumably owing to the difficulty of recovering enough of the Pd catalyst from cycle to cycle because of its solubility in the solvent.

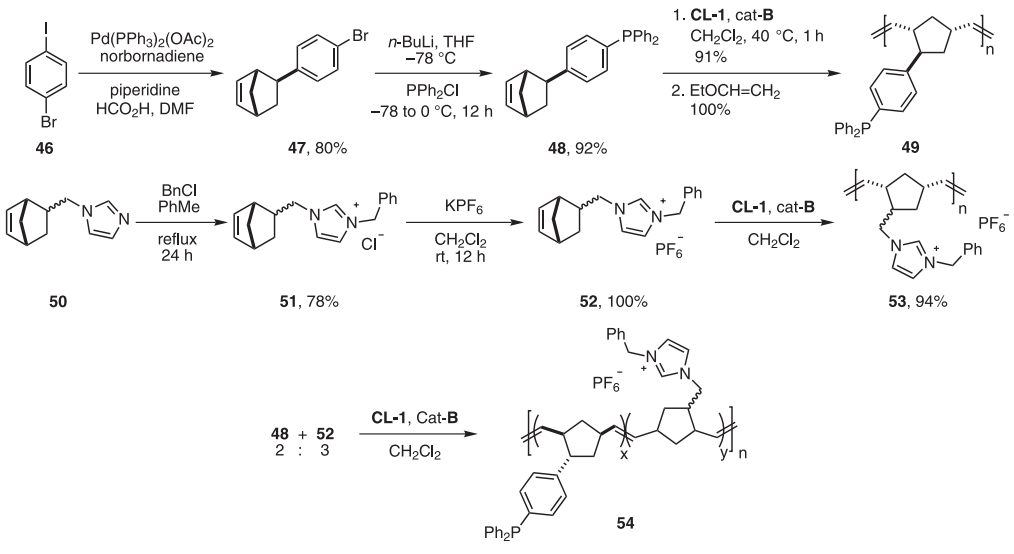
### 5.4. ROMPgel-Supported Thiazolium Iodide in Stetter Reactions

In 2004, Barrett and co-workers reported a high-load, ROMPgel-supported thiazolium iodide, that was prepared in three steps overall via ROM polymerization of the corresponding norbornene-derived monomer (**Scheme 11**).[42a] The Diels–Alder reaction between commercially available 4-methyl-5-vinyl-1,3-thiazole (**65**) and cyclopentadiene gave a 53% yield of a 1:9.5 mixture of exo and endo cycloadducts, **66**. Methylation of **66** with MeI gave the thiazolium salt monomer, **67**, which was polymerized with cat-**B** in the presence of cross-linker **CL-1** (11 mol %) to afford ROMPgel **68** possessing a theoretical load of 2.52 mmol/g.

Ionic ROMPgel **68** proved to be an efficient organic catalyst for Stetter reactions, especially for the reaction of aliphatic aldehydes with a range of enones (**eq 7**).[42a] The resulting 1,4-dicarbonyl products, which are important intermediates in the synthesis of cyclopentenones and heterocycles, were obtained in high yields and excellent purities after minimal purification. ROMPgel **68** maintained its catalytic activity, when used in up to four consecutive reaction cycles.

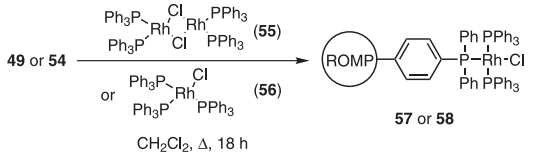
## 6. Purification by in Situ Polymerization

One purification strategy that has gained popularity in recent years is the use of chemically tagged reagents.[46] A chemical tag allows for the selective removal of reaction components (reagents, products, byproducts) through specific chemical interactions. Examples of chemical tagging strategies include: the fluorous-phase chemistry developed by Curran;[47] metal chelation as



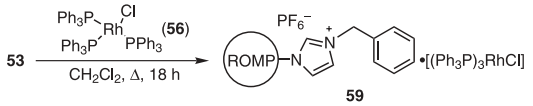

*Ref. 23,40*

**Scheme 9.** ROM Polymer-Supported Wilkinson's Catalyst.



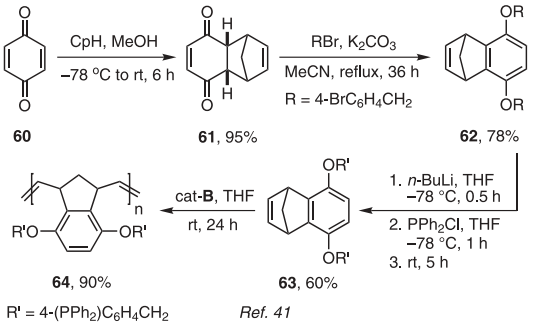

*Ref. 40*

**eq 2**



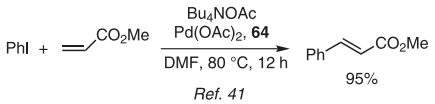

*Ref. 40*

**eq 3**



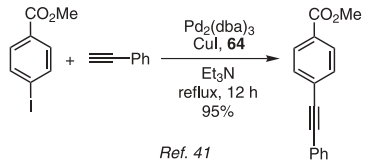

*Ref. 41*

**Scheme 10.** Preparation of Polymer-Supported Bisphosphine Ligand.



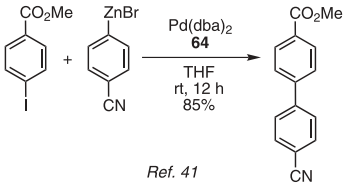

*Ref. 41*

**eq 4**



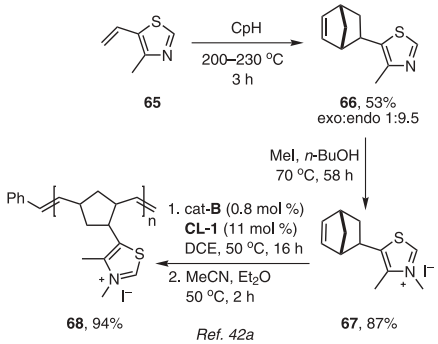

*Ref. 41*

**eq 5**



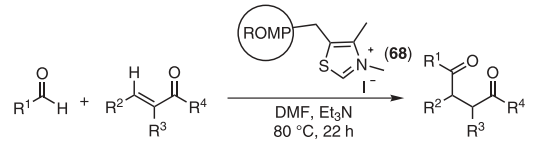

*Ref. 41*

**eq 6**




*Ref. 42a*

**Scheme 11.** Preparation of a High-Load, ROMPgel-Supported Thiazolium Iodide.

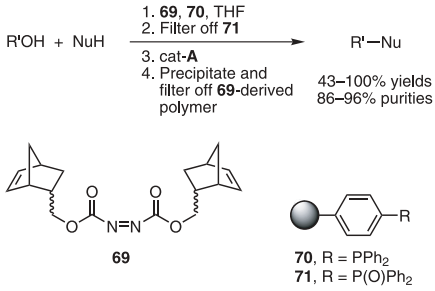



$R^1$ = 1° or 2° alkyl, Ph, heteroaryl
$R^2$ = (substituted) phenyl, H
$R^3$ = H, alkyl
$R^4$ = (substituted) aryl, alkyl

68–99% yields
66 to > 95% purities

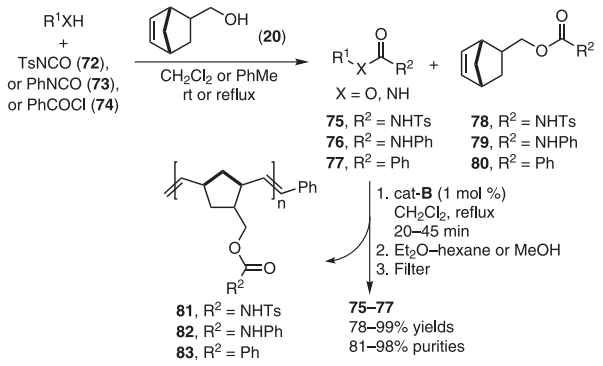
*Ref. 42a*

**eq 7**




*Ref. 51*

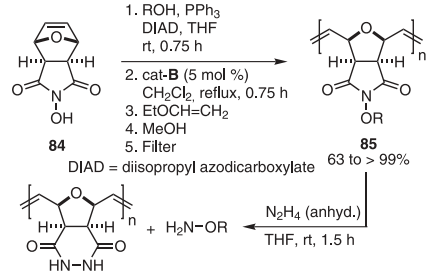
**Scheme 12.** Illustration of the Scavenge–ROMP–Filter Approach to Product Purification.




$R^1XH$ = 1°, 2°, or 3° ROH; ArOH; 1° or 2° amine

*Ref. 52*

**Scheme 13.** Scavenge–ROMP–Filter Approach to Purification of Reaction Mixtures.




R = Bn, 4-MeOC$_6$H$_4$CH$_2$, Ph(CH$_2$)$_3$, *trans*-PhCH=CHCH$_2$, (1-naphthyl)methyl, 1-tetrahydronaphthyl, (*S*)-2-octyl, (*E*)-3,7-Me$_2$-2,6-octadien-1-yl

*Ref. 53*

**Scheme 14.** Illustration of the Capture–ROMP–Release Approach to Product Purification.

reported by Ley;[48] and the precipiton tag developed by Wilcox's group,[49] which takes advantage of the light-induced isomerization and differential solubility of *cis*- and *trans*-stilbenes. When utilized in conjunction with the highly functional group tolerant olefin metathesis catalysts, the norbornene ring system offers attractive possibilities for use as a chemical tag. First, the ring system can be obtained on a large scale and in high yield through the use of Diels–Alder or reductive Heck reactions.[50] Secondly, the ring system is stable to many reaction conditions; and lastly, this strained olefin ring system can be selectively polymerized in the presence of other functional groups, and in some cases other olefins. For these reasons, in situ ROM polymerization is an appealing purification method that is not possible with other polymerization methods.

### 6.1. Reagent Annihilation: Norbornenyl-Tagged DEAD

Barrett was the first to report the use of in situ ROM polymerization of the norbornenyl-tagged azodicarboxylate **69** and polymer-bound triphenylphosphine (**70**) to purify Mitsunobu reactions (**Scheme 12**).[51] Upon completion of the reaction, **71** needed to be filtered away due to the incompatibility of the phosphine oxide polymer **71** with the soon-to-be-added cat-**A**. The hydrazine dicarboxylate byproduct was then polymerized by addition of cat-**A**. Subsequent filtration of the resulting diazodicarboxylate polymer afforded the Mitsunobu products in high yields and purities.

### 6.2. Scavenge–ROMP–Filter

Emergence of the more versatile cat-**B**[14] presented new opportunities for in situ scavenging, whereby norbornenyl-tagging was used to chemically tag electrophiles. Addition of cat-**B** initiated ROM polymerization, which ultimately phase-trafficked the resulting undesired polymeric species out of solution, leaving the reaction products in solution (**Scheme 13**).[52] To this end, an alcohol or an amine was reacted with an excess of an electrophilic reagent. Once the starting nucleophile was consumed, commercially available alcohol **20** was added as a scavenger to sequester excess electrophile. Upon completion of the scavenging event, cat-**B** was added in order to polymerize the scavenged electrophile, **78**–**80**, and excess alcohol **20**. The resulting polymer, **81**–**83**, was filtered away from the reaction products, **75**–**77**, which were subsequently isolated in excellent yields and purities.

### 6.3. Capture–ROMP–Release

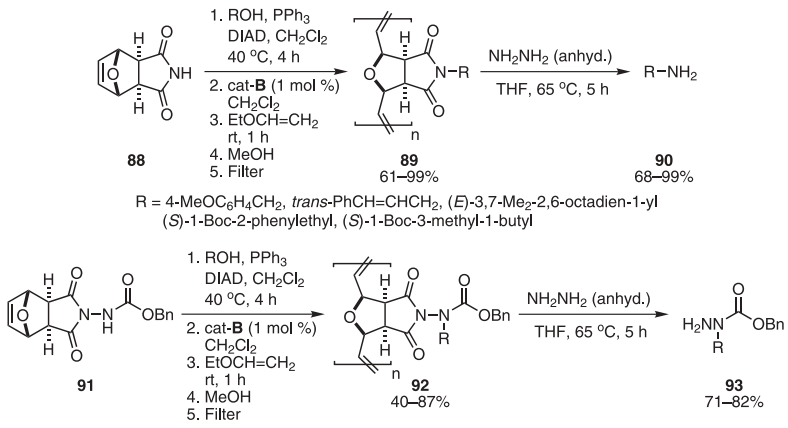
We have applied the in situ polymerization concept to the Mitsunobu reaction by targeting the acidic component/product (**Scheme 14**).[53] Commercially available oxanorbornenyl-tagged *N*-hydroxysuccinimide **84** was reacted with a variety of alcohols under traditional Mitsunobu conditions (DIAD and $PPh_3$). The resulting alkoxysuccinimides were then polymerized with cat-**B** in the presence of DIAD and $Ph_3PO$. The resulting polymers, **85**, were precipitated with MeOH, collected by filtration, and treated with hydrazine to release the desired alkoxyamines, **86**. Surprisingly, cleaved polymer **87** was water-soluble and was thus eliminated through a simple water–ether extraction.

We have also reported a similar strategy for the chromatography-free purification of amines and hydrazine derivatives (**Scheme 15**).[54] Various substituted alcohols were captured onto oxanorbornenyl derivatives **88** and **91** via the Mitsunobu reaction followed by in situ polymerization. Polymers **89** and **92** displayed differential solubility: soluble in organic solvents such as THF, $CH_2Cl_2$, and $CHCl_3$; but insoluble in MeOH. Excess Mitsunobu reagents and byproducts, which were soluble in MeOH, were phase-separated from the insoluble polymers via precipitation of the latter from MeOH, followed by simple filtration. The amines and hydrazine derivatives were cleaved from the polymers by heating at reflux in THF in the presence of hydrazine. Finally, the polymeric byproducts were removed by biphasic extraction ($Et_2O$–$H_2O$) to produce amines **90** and hydrazine derivatives **93** in good yields and purities.

## 7. ROM Polymerization in Supported Synthesis

### 7.1. Vanishing Supports, ROMPspheres, and Soluble Supports

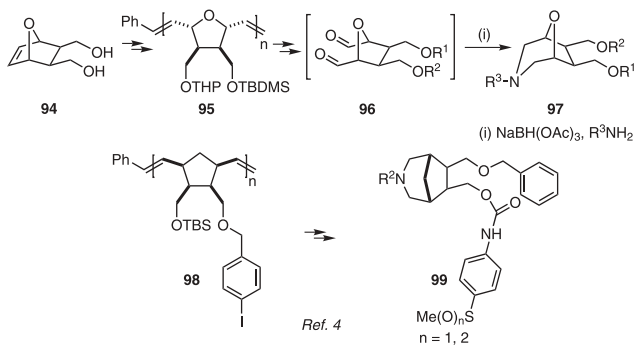
In 1998, Barrett and co-workers devised the concept of polymerizable templates and vanishing supports,[55] as outlined in **Schemes 16** and **17** and in their 2002 review.[4] This work addressed the classical problem of low loading of substrates on a polymer support. In addition, it offered the advantage of allowing chemical modifications to be conducted in a homogeneous environment, thus avoiding the poor solvation typically experienced with solid supports. In this approach, they produced diverse cyclic amines, **97** and **99**, in a strategy that employed late-stage ozonolysis as a means of disassembling the ROM polymer support. Subsequently, Barrett's group utilized two strategies in developing ROMPspheres. In the first, cross-metathesis between vinyl polystyrene and norbornene



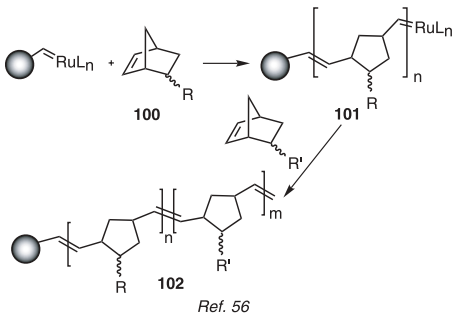

**Scheme 15.** Chromatography-Free Purification Employing the Capture–ROMP–Release Approach.

derivatives afforded high-load ROM polymer supports.[56] In the second approach, shown in Scheme 17, they incubated **100** with cat-**A** to obtain polystyrene-bound ruthenium complex **101**. ROMPsphere **102** was produced via subsequent treatment with norbornenyl monomer, followed by termination with EVE. The ROMPspheres were larger than the original resin, yet still retained their solvent-dependent swelling properties.[4]

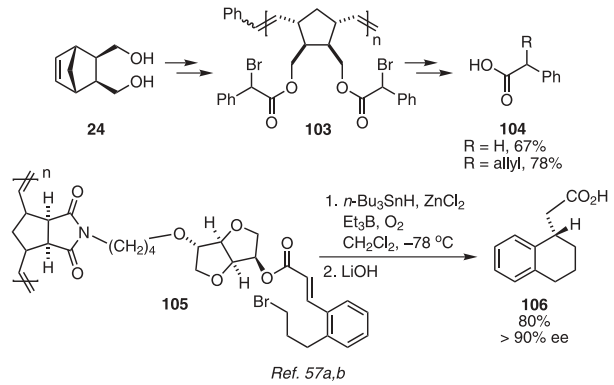
Enholm and co-workers reported the first examples of stereoselective radical reactions on a ROMP-derived, soluble support using norbornenediol **24** to assemble support **103** for subsequent radical allylation en route to **104** (**Scheme 18**).[57]




**Scheme 16.** Barrett's Vanishing Supports.




**Scheme 17.** Barrett's ROMPspheres.




**Scheme 18.** Enholm's High-load, Soluble Supports for Radical Transformations.

Another radical reaction was used in the $Bu_3SnH$-mediated cyclization of **105** which, upon saponification with LiOH, gave the carboxylic acid **106** in good yield. Each soluble support consisted of a radical precursor embedded in each monomer subunit, thus providing a maximum 100% loading capacity.

### 7.2. Ring-Opening-Metathesis–Phase-Trafficking (ROMpt) Synthesis

The aforementioned capture–ROMP–release approach has also been utilized as a means of generating ROM oligomers for subsequent use as soluble supports in multistep reaction sequences (**Scheme 19**).[58] In this strategy, norbornene sulfonamide **107** was subjected to a three-component coupling protocol with chlorosulfonyl isocyanate and an amino acid ester to yield **108**. The tagged norbornenyl monomer was next reacted with cinnamyl alcohol under Mitsunobu conditions. The norbornenyl tagged products were then induced to undergo phase-trafficking purification by in situ polymerization mediated by cat-**B**. Quenching of the polymerization with ethyl vinyl ether, followed by precipitation of the oligomers with methanol, provided oligomers **109**, free of Mitsunobu byproducts. The terminal phenyl group was utilized as a protecting group of the double bond during the ROM polymerization event. Allylation of the soluble oligomer yielded **110**, which was subjected to RCM conditions to generate **111**. Purification was achieved by differential precipitation of the oligomer. Finally, oligomer **111** was treated with 1:1 TFA–$CH_2Cl_2$ to effect the release of cyclic sulfamide **112** from the soluble support, whereby the crude products were passed through a small SPE ($SiO_2$) and eluted with 1:1 hexane–ethyl acetate (49–53% over four steps).

### 7.3. Oxidative Cyclorelease Strategy Using Soluble ROM Polymer Supports

Floreancig and co-workers have also utilized soluble oligonorbornene polymers as supports in an oxidative cyclorelease strategy, where the soluble supports were found to be stable toward redox chemistry (**Scheme 20**).[59] Monomer **113** was polymerized utilizing 5 mol % cat-**A** to provide oligomer **114** in 95% yield. Oligomer **114** was subjected to a three-step sequence of $TiCl_4$–$Ti(O\textit{i}\text{-}Pr)_4$-mediated acetal opening, ruthenium-catalyzed acetic acid addition, and TBS protection to yield enol acetate polymer **115** in high yield. Cyclorelease of **115** with CAN provided **116** as a single stereoisomer in 41% yield and good purity.[59]

### 7.4. Unsaturated ROMP (U-ROMP) Resins

Janda and co-workers have employed a technique termed suspension-ROMP to construct insoluble, spherical resins with good swelling properties for use in solid-phase organic synthesis (**Scheme 21**).[60] It was found that 1 mol % of cross-linker **117** gave optimal results in terms of swelling properties, with alcohol **20** being present in 1 mmol/g theoretical loading. The swelling properties of unsaturated ROMP resin (U-ROMP) **118** were intermediate between those of the Merrifield and *J*anda*J*el™ resins.

U-ROMP resin **118** was subjected to hydrogenation, bromination, chlorination, and hydrofluorination conditions to remove the olefinic backbone. The authors were then able to use these new norbornene-based resins for reactions that are incompatible with traditional cross-linked polystyrene resins (i.e., Friedel–Crafts acylations and aromatic nitration). They also reported utilizing these resins for two multistep SPS reaction sequences: the synthesis of benzimidazole and hydantoin derivatives.[60]

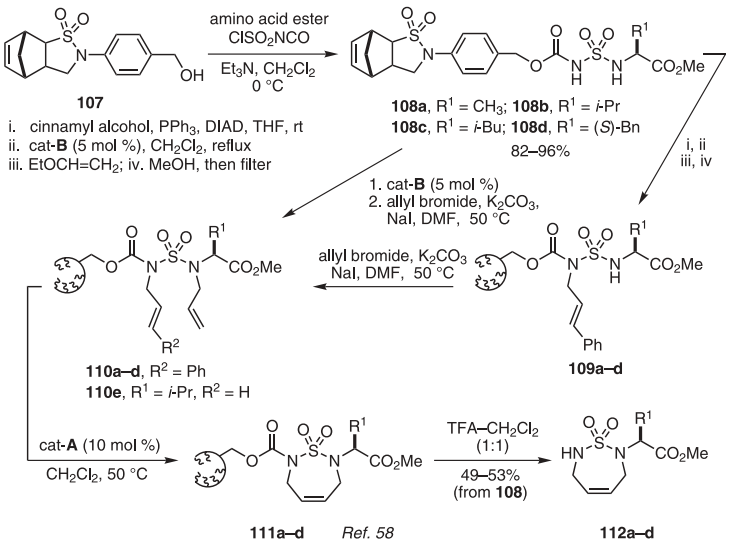
## 8. New Strategies Employing ROM Polymerization

### *8.1. Polymer-on-Polymer Approach*

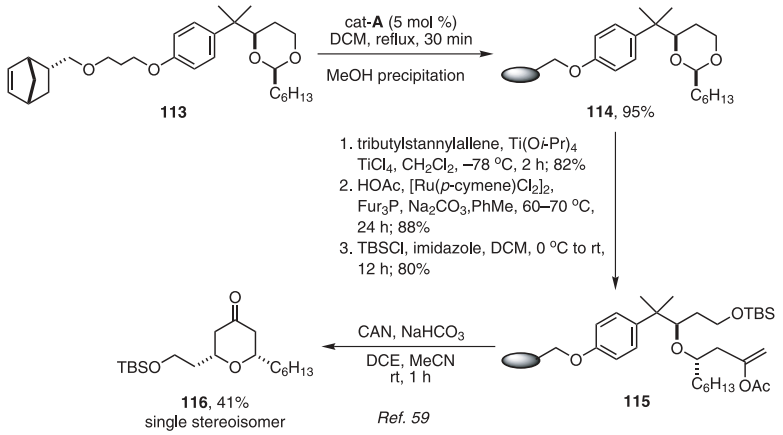
Recently, we have dramatically demonstrated the power of soluble ROM polymers with the realization of the first polymer-on-polymer Mitsunobu reaction, in which a polymeric phosphine is used *simultaneously* with a polymeric azodicarboxylate (**Scheme 22**).[61] Historically, the Mitsunobu reaction has faced a number of purification challenges,[62] and popular opinion has asserted that a multipolymer, solid-on-solid approach is not feasible.[62b] The use of high-load, short, and soluble oligomers, however, circumvents classical problems associated with solid-on-solid approaches. The oligomeric triphenylphosphine (OTPP, **119**) was prepared through polymerization of phosphine **48** with cat-**B** (see Scheme 22). The required hydrogenated oligomeric azodicarboxylate (HO-DEAD, **121**) was prepared from alcohol **120**. The hydrazine dicarboxylate generated from **120** was polymerized with cat-**F**, and the resulting polymer hydrogenated in the presence of cat-**A**, prior to oxidation with $Br_2$, to give **121**. Both **119** and **121** display a wide solubility profile: they are soluble in benzene, toluene, $CH_2Cl_2$, $CHCl_3$, and THF; but insoluble in MeOH, $Et_2O$, and heptane. $^{31}P$ NMR analysis revealed that the two polymers were interacting to generate the Mitsunobu products. In addition, application of this approach to several other substrates, as well as comparison experiments with other polymeric reagents, have been described.[61]

### *8.2. ROMPgel Beads in IRORI℠ Format*

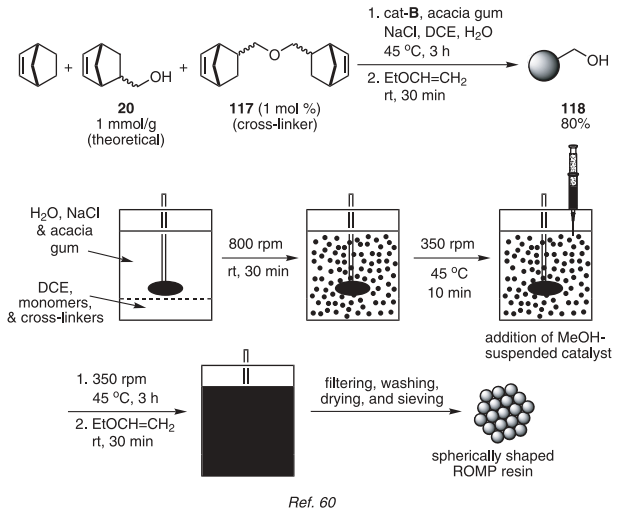
Roberts recently integrated the convenience of handling polystyrene beads in an IRORI℠ KAN™ format with high-load ROMPgels to generate a reusable acylating agent for parallel synthesis (**Scheme 23**).[63] The high load and site accessibility of the ROMPgel resin was not compromised by incorporation into a bead, while the convenience of a KAN™ format was added. Thus, linker **122** was synthesized from 4-iodophenol via hydroarylation of norbornadiene. Linker **122** was attached to Wang resin (1.1 mmol/g) utilizing Mitsunobu conditions to afford linker resin **123** in 79% yield. The norbornene moiety in the linker was subjected to ROM polymerization conditions with cat-**A**. After washing the resin to remove excess unreacted catalyst in solution, it was treated with a large excess of monomer **124** for 48 h yielding resin **125** in 94% yield with a loading of 2.92 mmol/g. Treating resin **125** with an excess of benzylamine and washing with 15%




**Scheme 19.** Application of Ring-Opening-Metathesis–Phase-Trafficking (ROMpt) in Supported Synthesis.

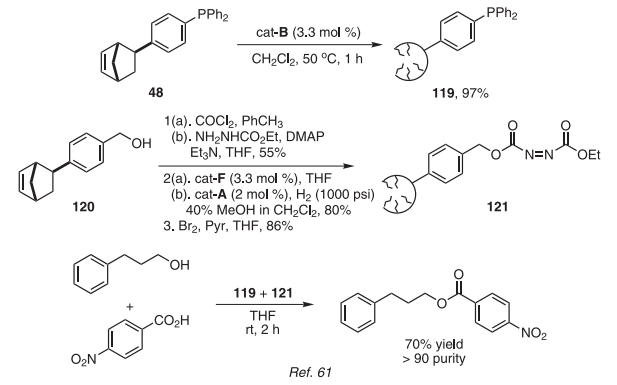



**Scheme 20.** Application of Soluble Oligonorbornene Polymers as Supports in an Oxidative Cyclorelease Strategy.



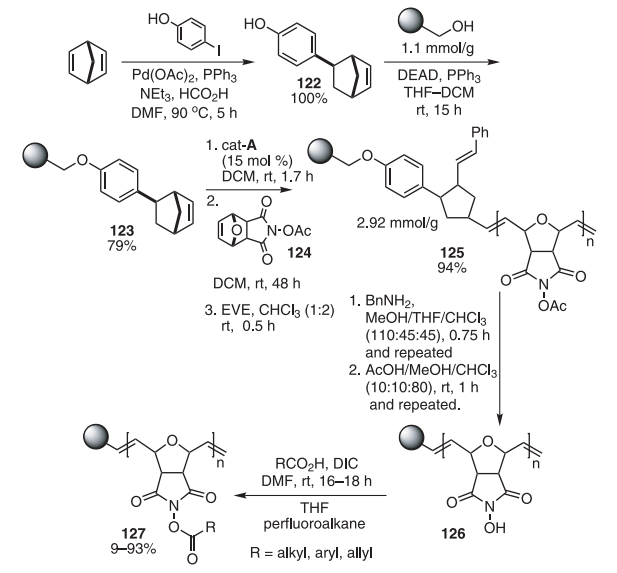

*Ref. 60*

**Scheme 21.** Preparation of Spherical, Unsaturated ROMP (U-ROMP) Resins by Suspension-ROMP.




*Ref. 61*

**Scheme 22.** Application of the Polymer-on-Polymer Approach in the Mitsunobu Reaction.




*Ref. 63*

**Scheme 23.** ROMPgel Beads in IRORI[SM] Format: High-Load and Reusable Acylating Agents.

AcOH in dichloromethane generated *N*-hydroxysuccinimide resin **126**, which was coupled with a variety of carboxylic acids to produce an array of high-load acylating agents **127**.

## 9. Conclusions

This review has outlined new developments of ROM polymerization in facilitated synthesis. From its beginning, ROM polymerization has advanced as a general and viable means of immobilizing reagents, catalysts, and supports, and will undoubtedly expand beyond these borders in the near future. The continued development of well-defined, homogeneous catalysts can only add to the growing utility of this enabling technology, and thus its potential has yet to be fully realized. In addition, automated protocols have yet to be fully adapted to this technology, which will only further strengthen its role in combinatorial chemistry.

## 10. Acknowledgements

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(33) The oligomeric reagents are abbreviated according to the "generation" of Grubbs' catalyst used for the polymerization (the superscript before the abbreviation) and the length of the polymer (the subscript following the abbreviation). Thus, $^{2G}OACC_n$ stands for n-mer OACC (oligomeric alkyl cyclohexyl carbodiimide), where n = 50, 100, 150. These are prepared by ROM polymerization of monomer carbodiimide **32** using second-generation (2G) Grubbs' catalyst (cat-**B**).

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## About the Authors

**Andrew M. Harned** graduated from Virginia Polytechnic Institute and State University (Virginia Tech) in 1999 with a B.S. in biochemistry. While an undergraduate, he worked in the laboratories of Professors Neal Castagnoli, Jr., and Michael Calter. As a graduate student at the University of Kansas, he studied under the guidance Professor Paul R. Hanson. While at KU, he was supported by an NIH Dynamic Aspects of Chemical Biology Training Grant and an American Chemical Society Division of Organic Chemistry Nelson J. Leonard Fellowship sponsored by Organic Syntheses, Inc. In the fall of 2004, he assumed a postdoctoral position in the research group of Professor Brian M. Stoltz at the California Institute of Technology.

**Mianji Zhang** received his M.S. degree in organic chemistry in 1992 from Nankai University (China). After working in Tianjin University in China for five years, he joined Professor Robert T. LaLonde's group at the State University of New York, College of Environmental Science & Forestry (SUNY-ESF) in 1997. He worked on the synthesis of antitumor drug candidates and completed the requirements for his Ph.D. degree in 2002. He is currently a postdoctoral research associate working on the development of ROMP-derived high-load reagents under the guidance of Professor Paul R. Hanson at the University of Kansas.

**Punitha Vedantham** obtained her master's degree in 1996 from the Indian Institute of Technology in Delhi, India. Her doctoral studies on natural product synthesis and organic photochemistry were carried out at the Indian Institute of Technology, Bombay, under the guidance of Professor Vishwakarma Singh. She is currently working with Professor Paul R. Hanson on ROM polymerization and facilitated synthetic methods for use in combinatorial chemistry.

**Shubhasish Mukherjee** graduated from the Indian Institute of Technology, Delhi, with an M.Sc. degree in chemistry. He received his Ph.D. degree in chemistry in 2000 from the University of Delhi, India, for research and studies carried out under the guidance of Professor V. S. Parmar. He worked for a year in the area of bioconjugate chemistry with Professor Kalle Levon at The Polytechnic University, New York. In 2001, he moved to the University of Kansas, where he is currently working for Professor Paul R. Hanson in the area of ROM polymerization and phosphorus chemistry.

**Russell H. Herpel** graduated from Missouri Western State College in 1997 with an ACS certified B.S. degree in chemistry. In the summer of 1996, he worked for Professor Rich Givens at the University of Kansas in the National Science Foundation Research Experience for Undergraduates (NSF-REU) Program. He then carried out graduate-level studies at the University of Kansas under the guidance of Professors Rich S. Givens (1997–2000) and Paul R. Hanson (2002–2004). In the fall of 2004, he assumed a position at Highland Community College as a chemistry instructor.

**Daniel L. Flynn** received his B.S. degree in pharmacy (1977) and his Ph.D. degree in medicinal chemistry (1981, with Professor Lester Mitscher) from the University of Kansas. After completing postdoctoral studies at Indiana University with Professor Paul Grieco, he joined Warner-Lambert/Parke-Davis Pharmaceuticals in 1983. In 1988, he moved to Searle Pharmaceuticals, where he rose to the positions of Section Head, Medicinal Chemistry, and Research Fellow over a ten-year period. Between 1998 and 2002, he was engaged in research at Amgen, Inc., and Millennium Pharmaceuticals as senior director of chemistry. In 2002, he founded Deciphera Pharmaceuticals, Inc., where he has remained as its president and CEO. His research interests include phase-trafficking approaches to organic synthesis and purification, chemical proteomics, and innovative ways to selectively control enzymatic activity by binding small molecules onto novel allosteric sites.

**Paul R. Hanson** received his B.S. degree, with a major in chemistry, in 1985 from Luther College (Decorah, IA) under the direction of the late Adrian Docken. In 1993, he obtained his Ph.D. in chemistry from the University of Minnesota under the mentorship of Thomas R. Hoye. From 1993 to 1996, he served as an NIH postdoctoral fellow at Stanford University under the guidance of Barry M. Trost. In 1996, he was hired as an assistant professor of chemistry at the University of Kansas and was promoted to associate professor in 2001. His current research interests lie in the development of new approaches to the synthesis of biologically and synthetically useful phosphorus and sulfur heterocycles, natural product synthesis, and the design of high-load oligomers with tunable properties for use in facilitated synthesis.

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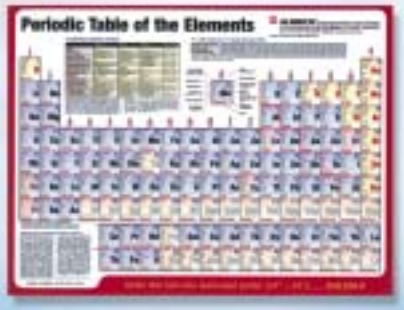

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Solid-supported reagents have been utilized in a variety of ways to facilitate combinatorial synthesis. They are also being used in solution-phase parallel synthesis and multistep organic synthesis as scavengers to ease reaction workup and product purification.[1] One important specification for solid-supported reagents is loading. A high loading for scavenger resins allows for decreased reaction workup volume.

Sigma-Aldrich is proud to offer a line of resins called Rasta Resins. These resins have increased loading with minimal swelling. For most solid-supported reagents, the functional groups are attached to polystyrene that is cross-linked with divinylbenzene. A nonpolar solvent is normally required to swell the polystyrene beads, which allows more attachment sites to be exposed. The unique bead structure of the Rasta Resin has a long and linear polymer chain connected to a nonfunctionalized, cross-linked core that allows for increased functional-group loading, spacing, and accessibility with minimal swelling.[2]

One example of increased loading is isocyanate on Rasta Resin. The maximum loading for methyl isocyanate on polystyrene is typically 1.0–1.5 mmol/g; for isocyanate on Rasta Resin it is 2.0 mmol/g.

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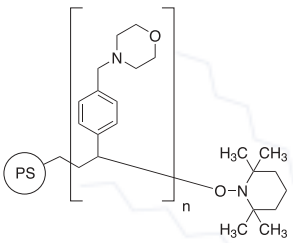
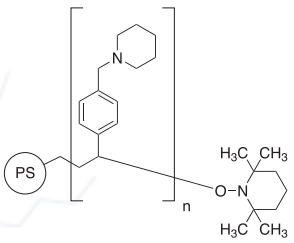
**References:** (1) Ley, S. V. et al. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815. (2) Hodges, J. C. et al. *J. Comb. Chem.* **2000**, *2*, 80.

## Rasta Resin Bases

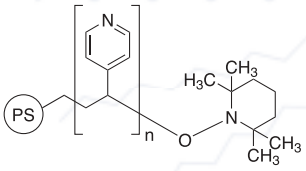
**64,359-9**
Morpholine on Rasta Resin
50–100 mesh, 5.0 mmol/g loading, 1% cross-linking
5 g
25 g




**64,360-2**
Piperidine on Rasta Resin
50–100 mesh, 5.0 mmol/g loading, 1% cross-linking
5 g
25 g

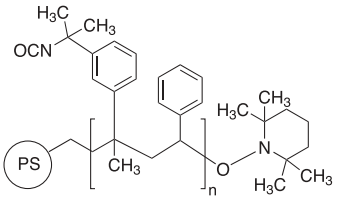



**65,545-7**
Pyridine on Rasta Resin
50–100 mesh, 6.9 mmol N/g loading, 1% cross-linking
5 g
25 g

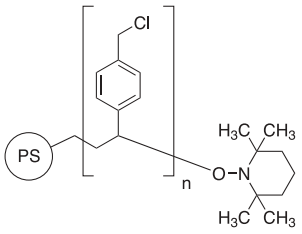



## Rasta Resin Scavengers

**56,966-6**
Isocyanate on Rasta Resin
100–200 mesh, 2.0 mmol/g loading, 1% cross-linking
5 g
25 g



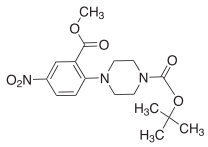

**64,366-1**
Chloromethyl on Rasta Resin
50–100 mesh, 5.0 mmol/g loading, 1% cross-linking
5 g
25 g



# New Piperazine Building Blocks from Sigma-Aldrich

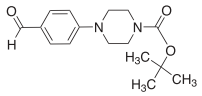
### 1-Boc-4-(2-methoxycarbonyl-4-nitrophenyl) piperazine, 97%

**65,193-1** 1 g
MW 365.38 5 g
$C_{17}H_{23}N_3O_6$



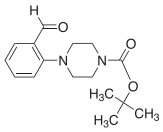
### 1-Boc-4-(4-formylphenyl)piperazine, 97%

**65,142-7** 1 g
MW 290.36 5 g
$C_{16}H_{22}N_2O_3$



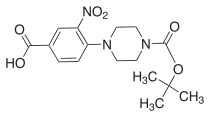
### 1-Boc-4-(2-formylphenyl)piperazine, 97%

**65,151-6** 1 g
MW 290.36 5 g
$C_{16}H_{22}N_2O_3$



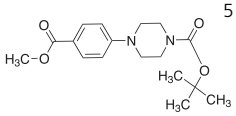
### 4-(Boc-piperazin-1-yl)-3-nitrobenzoic acid, 97%

**65,192-3** 1 g
MW 351.35 5 g
$C_{16}H_{21}N_3O_6$



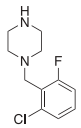
### 1-Boc-4-(4-methoxycarbonylphenyl)piperazine, 97%

**65,238-5** 1 g
MW 320.19 5 g
$C_{17}H_{24}N_2O_4$



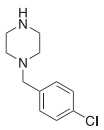
### 1-(2-Chloro-6-fluorobenzyl)piperazine, 98%

**65,015-6** 1 g
MW 228.69 10 g
$C_{11}H_{14}ClFN_2$



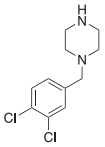
### 1-(4-Chlorobenzyl)piperazine, 98%

**65,021-8** 1 g
MW 210.70 5 g
$C_{11}H_{15}ClN_2$



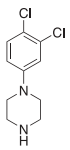
### 1-(3,4-Dichlorobenzyl)piperazine, 97%

**64,426-9** 1 g
MW 245.15 5 g
$C_{11}H_{14}Cl_2N_2$



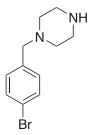
### 1-(3,4-Dichlorophenyl)piperazine, 99%

**55927** 5 g
MW 231.12 25 g
$C_{10}H_{11}Cl_2N_2$



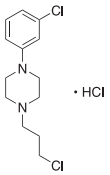
### 1-(4-Bromobenzyl)piperazine, 97%

**04695** 1 g
MW 255.15 5 g
$C_{11}H_{15}BrN_2$



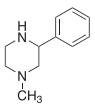
### 1-(3-Chlorophenyl)-4-(3-chloropropyl)piperazine monohydrochloride, 97%

**16843** 5 g
MW 309.66 25 g
$C_{13}H_{19}Cl_3N_2$



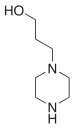
### 1-Methyl-3-phenylpiperazine, 97%

**64,843-4** 1 g
MW 176.26 5 g
$C_{11}H_{16}N_2$



### 1-(3-Hydroxypropyl)piperazine, 97%

**64,164-2** 1 g
MW 144.21 5 g
$C_7H_{16}N_2O$

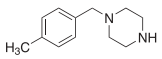


### 2-Phenylpiperazine, 96%

**63,864-1** 5 g
MW 162.23 25 g
$C_{10}H_{14}N_2$

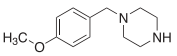
### 1-(4-Methylbenzyl)piperazine, 97%

**64,617-2** 1 g
MW 190.28 5 g
$C_{12}H_{18}N_2$



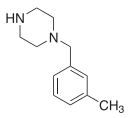
### 1-(4-Methoxybenzyl)piperazine, 97%

**64,615-6** 1 g
MW 206.28 5 g
$C_{12}H_{18}N_2O$



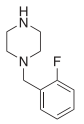
### 1-(3-Methylbenzyl)piperazine, 97%

**64,852-3** 1 g
MW 190.28 5 g
$C_{12}H_{18}N_2$



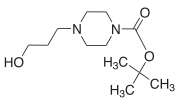
### 1-(2-Fluorobenzyl)piperazine, 96%

**65,024-2** 1 g
MW 194.25 5 g
$C_{11}H_{15}FN_2$



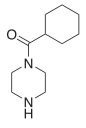
### 1-Boc-4-(3-hydroxypropyl)piperazine, 97%

**64,346-7** 5 g
MW 244.33 25 g
$C_{12}H_{24}N_2O_3$



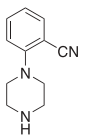
### 1-(Cyclohexylcarbonyl)piperazine, 97%

**64,712-8** 1 g
MW 196.29 5 g
$C_{11}H_{20}N_2O$



### 2-(2-Cyanophenyl)piperazine, 99%

**56,718-3** 1 g
MW 187.24 5 g
$C_{11}H_{13}N_3$



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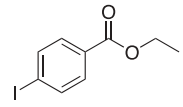
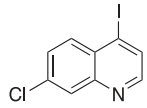
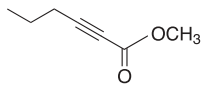
**Ethyl 4-iodobenzoate, purum, 98%**
**75022** 10 g



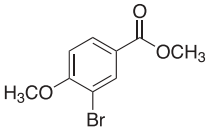
**7-Chloro-4-iodoquinoline, 97%**
**64,738-1** 1 g, 10 g



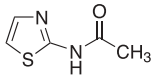
**Methyl 2-hexynoate, 98%**
**64,909-0** 5 g, 25 g



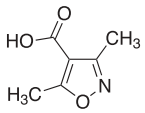
**Methyl 3-bromo-4-methoxybenzoate, 98%**
**64,757-8** 1 g, 10 g



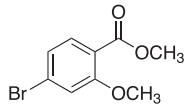
**2-Acetamidothiazole, purum, 98%**
**65,295-4** 5 g



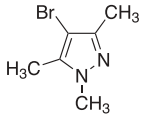
**3,5-Dimethylisoxazole-4-carboxylic acid, puriss., 98%**
**65,287-3** 1 g, 5 g



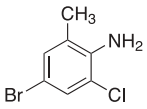
**Methyl 4-bromo-2-methoxybenzoate, puriss., 98%**
**65,309-8** 1 g, 10 g



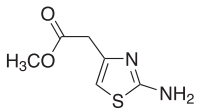
**4-Bromo-1,3,5-trimethylpyrazole, 98%**
**64,766-7** 1 g, 5 g



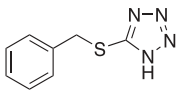
**4-Bromo-2-chloro-6-methylaniline, puriss., 98%**
**65,293-8** 5 g, 25 g



**Methyl (2-amino-4-thiazolyl)acetate, 98%**
**64,972-4** 1 g, 5 g



**5-(Benzylthio)-1*H*-tetrazole solution, ~0.25 M in acetonitrile**
**16998** 100 mL, 500 mL



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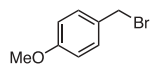
## Organic Reagents and Building Blocks

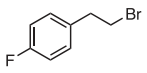
### 4-Methoxybenzyl bromide

**56,128-2** 5 g
$C_8H_9BrO$



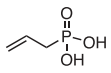

### 4-Fluorophenethyl bromide

**65,200-8** 5 g
$C_8H_8BrF$



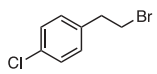

### Allylphosphonic acid

**65,398-5** 250 mg, 1 g
$C_3H_7O_3P$



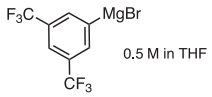

### 4-Chlorophenethyl bromide

**65,199-0** 5 g
$C_8H_8BrCl$



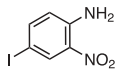

### 3,5-Bis(trifluoromethyl)phenylmagnesium bromide solution, 0.5 M in THF

**63,905-2** 50 mL
$C_7H_4BrF_6Mg$




### 4-Iodo-2-nitroaniline

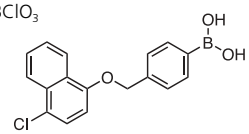
**65,410-8** 1 g, 10 g
$C_6H_5IN_2O_2$




## Boronic Acids and Esters

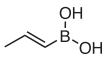
### 4-[(4′-Chloro-1-naphthyloxy)methyl]phenylboronic acid

**64,565-6** 1 g, 5 g
$C_{17}H_{14}BClO_3$



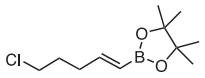

### *trans*-Propenylboronic acid

**57,663-8** 1 g, 5 g
$C_3H_7BO_2$



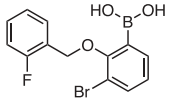

### (*E*)-5-Chloro-1-pentenylboronic acid, pinacol ester

**65,206-7** 5 g, 25 g
$C_{11}H_{20}BClO_2$



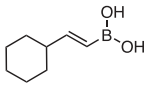

### 3-Bromo-2-(2′-fluorobenzyloxy)phenylboronic acid

**64,583-4** 1 g, 5 g
$C_{13}H_{11}BBrFO_3$



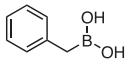

### 2-Cyclohexylvinylboronic acid

**59,625-6** 1 g, 10 g
$C_8H_{15}BO_2$



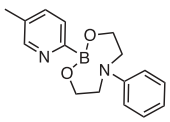

### Benzylboronic acid

**65,235-0** 1 g, 5 g
$C_7H_9BO_2$



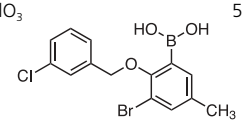

### 5-Methyl-2-pyridineboronic acid, *N*-phenyldiethanolamine ester

**64,882-5** 500 mg, 1 g, 5 g
$C_{16}H_{19}BN_2O_2$



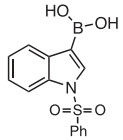

### 3-Bromo-2-(3′-chlorobenzyloxy)-5-methylphenylboronic acid

**64,549-4** 1 g, 5 g
$C_{14}H_{13}BBrClO_3$



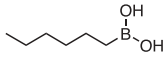

### 1-(Phenylsulfonyl)-3-indoleboronic acid

**56,387-0** 1 g
$C_{14}H_{12}BNO_4S$




### Hexylboronic acid

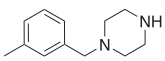
**65,159-1** 1 g, 5 g
$C_6H_{15}BO_2$



# Heterocyclic Building Blocks

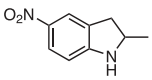
### 1-(3-Methylbenzyl)piperazine, 97%

**64,852-3** 1 g
$C_{12}H_{18}N_2$ 5 g



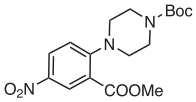
### 2-Methyl-5-nitroindoline

**64,984-8** 1 g
$C_9H_{10}N_2O_2$ 5 g



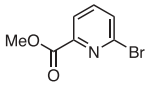
### Methyl 2-(4-Boc-piperazin-1-yl)-5-nitrobenzoate

**65,193-1** 1 g
$C_{17}H_{23}N_3O_6$ 5 g



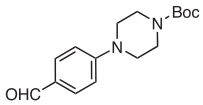
### Methyl 6-bromo-2-pyridinecarboxylate, 97%

**65,011-0** 1 g
$C_7H_6BrNO_2$ 5 g



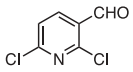
### 1-Boc-4-(4-formylphenyl)piperazine

**65,142-7** 1 g
$C_{16}H_{22}N_2O_3$ 5 g



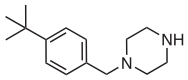
### 2,6-Dichloropyridine-3-carboxaldehyde

**65,195-8** 1 g
$C_6H_3Cl_2NO$ 5 g



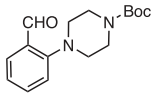
### 1-(4-*tert*-Butylbenzyl)piperazine

**65,012-9** 1 g
$C_{15}H_{24}N_2$ 5 g



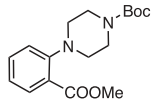
### 1-Boc-4-(2-formylphenyl)piperazine

**65,151-6** 1 g
$C_{16}H_{22}N_2O_3$ 5 g



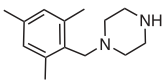
### 1-Boc-4-(2-methoxycarbonylphenyl)piperazine

**65,237-7** 1 g
$C_{17}H_{24}N_2O_4$ 5 g



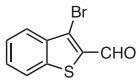
### 1-(2,4,6-Trimethylbenzyl)piperazine

**65,168-0** 1 g
$C_{14}H_{22}N_2$ 5 g



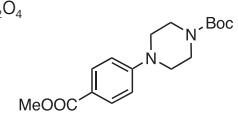
### 3-Bromobenzothiophene-2-carboxaldehyde

**65,153-2** 1 g
$C_9H_5BrOS$ 5 g



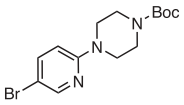
### 1-Boc-4-(4-methoxycarbonylphenyl)piperazine

**65,238-5** 1 g
$C_{17}H_{24}N_2O_4$ 5 g



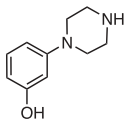
### 4-Boc-1-(5-bromo-2-pyridyl)piperazine

**65,376-4** 1 g
$C_{14}H_{20}BrN_3O_2$ 5 g



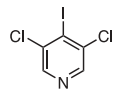
### 1-(3-Hydroxyphenyl)piperazine

**65,167-2** 1 g
$C_{10}H_{14}N_2O$ 5 g



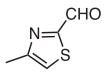
### 3,5-Dichloro-4-iodopyridine, 97%

**65,313-6** 1 g
$C_5H_2Cl_2IN$ 10 g



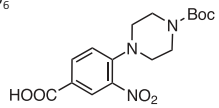
### 4-Methyl-2-thiazolecarboxaldehyde

**64,974-0** 1 g
$C_5H_5NOS$ 5 g



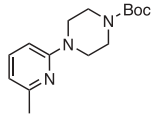
### 4-(4-Boc-piperazin-1-yl)-3-nitrobenzoic acid

**65,192-3** 1 g
$C_{16}H_{21}N_3O_6$ 5 g



### 4-Boc-1-(6-methyl-2-pyridyl)piperazine

**65,375-6** 1 g
$C_{15}H_{23}N_3O_2$ 5 g



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- Temp. range: ambient to 450 °C
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- CE compliant

### Sigma-Aldrich hot plate stirrer

| | |
|---|---|
| 115 Volts | **Z55,784-6** |
| 230 Volts | **Z55,818-4** |

### Digital temperature controller

Fuzzy logic control provides constant feedback to hot plate to ensure perfect temperature control of the medium without overshooting the set temperature. Connects to above stirring hot plates with a DIN 12878 socket. Includes a 250-mm (l) × 3-mm (o.d.) stainless steel temperature probe.

**Z55,785-4**

### Mounting hardware

Order one of each item to mount temperature controller onto hot plate stirrer.

| | |
|---|---|
| *Vertical support rod*<br>stainless steel rod threads into top of stirrer base | **Z40,356-3** |
| *Boss head clamp* | **Z40,357-1** |
| *Holding rod for controller* | **Z40,359-8** |

### Sigma-Aldrich hot plate stirrer sets

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| | |
|---|---|
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## Outline



## 1. Introduction

The cross-coupling of organic halides with organometallic reagents mediated by transition-metal catalysts has become a pivotal approach for carbon–carbon-bond formation. Organotin,[1] organoboron,[2] organozinc,[3] and organosilicon[4] are all useful precursors that are commonly employed in palladium-catalyzed cross-couplings.

The need for a practical and economic translation of these laboratory methods into large-scale manufacturing operations, coupled with the drive for clean manufacturing processes, have led to the development of new techniques for reagent and catalyst immobilization. These new techniques allow for the efficient recovery and reuse of the catalyst.[5] For example, the pharmaceutical industry anticipates ever more demanding API targets that require ever lower levels of metal residues from reaction catalysts.

The traditional heterogeneous transition-metal catalyst consists of a metal adsorbed on a variety of high-surface-area support materials such as silica, alumina, calcium carbonate, barium sulfate, powdered KF with $Al_2O_3$,[6a] poly(ethyleneimine) on alumina[6b] or silica,[6c] and so on. For these traditional adsorbed-

metal supports, the usual role of the support is to extend the surface area of the metal, although the nature of the support can significantly alter the rate and course of a chemical reaction.

In recent years, there has been significant development work reported on the synthesis and use of supported transition-metal catalysts[7a] produced by coordination of the metal to an immobilized ligand.[7b] These catalyst systems are often referred to as "supported" or "polymer-anchored" homogeneous catalysts. For example, Fenger and Le Drian introduced a polystyrene-supported palladium catalyst for use in the Suzuki cross-coupling reaction.[8] More recently, Ikegami and co-workers have reported a supported palladium catalyst for the Suzuki–Miyaura reaction, which is based on the non-cross-linked amphiphilic copolymer poly(*N*-isopropylacrylamide-*co*-4-(diphenylphosphino)styrene).[9,10] Industrial activity in this area has been led by workers at Johnson Matthey, who, in collaboration with Oy Smoptech, have developed immobilized, homogeneous palladium catalysts through the use of polyethylene fibers with grafted phosphine ligands.[11]

In general, these approaches require the synthesis of polymer-bound ligands either through copolymerization of a ligand monomer or postgrafting of a ligand onto a preformed polymer matrix. Such methodologies tend to be lengthy and expensive, and there can be problems associated with leaching and reactivity of the resulting catalyst.

An alternative approach for entrapping homogeneous catalysts within a polymeric coating has been developed by Kobayashi and co-workers.[12–14] Microcapsules of polymer-coated catalyst are formed upon cooling a homogeneous solution of the catalyst and a polymer or copolymer. This technique was exploited in the preparation of polystyrene-coacervated $OsO_4$,[12] $Pd(Ph_3)_4$,[13] and $Sc(OTf)_3$.[14] However, Schager and Bonrath reported that the coacervated $Sc(OTf)_3$ catalyst could not be recovered following use, and that there was evidence for leaching of the catalyst. The authors concluded that the catalytically active compound works as a homogeneous species.[15] More recently, Kobayashi and co-workers have further developed this technique by building a reactive oxirane functionality into the copolymer.[16] In this case, following coacervation of the homogeneous catalyst, the copolymer can be cross-linked thermally to form more chemically resistant cross-linked microcapsules. This technique has been exploited to form so-called "polymer-incarcerated" homogeneous $Pd(Ph_3)_4$ catalysts.[16]

Various other methods and materials have been described in the literature for entrapping homogeneous metal complexes and metal nanoclusters including sol-gel materials,[17] dendrimers,[18] and polyoxyalkylene resins.[19]

The purpose of this article is to review the area of microencapsulated palladium catalysts prepared by interfacial polymerization, which promises to be one of the most useful developments for immobilizing homogeneous catalysts to have originated over the past few years. We have, in collaboration with Professor Steven Ley, pioneered the technique based on interfacial microencapsulation to immobilize homogeneous transition-metal salts, and have demonstrated the application of these as versatile catalysts. This review will cover all aspects of catalyst preparation, physical properties, and applications.

## 2. Microencapsulation

In 2002, Ley and co-workers first reported the use of interfacial microencapsulation to immobilize homogeneous catalysts, suggesting that it might solve problematic limitations of previous approaches.[20] Microencapsulation is a process for entrapping materials within a shell or coating, which is typically polymeric in nature. Microencapsulation is widely practiced industrially and has found use in such diverse applications as drug delivery systems,[21] radiation therapies,[22] cell entrapment,[23] and the controlled release of pesticides.[24,25]

Ley utilized the interfacial microencapsulation method, which involves dispersing an organic phase (consisting of the material(s) being encapsulated and reactive multifunctional monomers or oligomers, and typically containing a solvent) into an aqueous phase containing colloid stabilizers, dispersants and, optionally, salts and chain extenders. Upon dispersion, the reactive groups at the oil–water interface undergo spontaneous in situ polymerization to form the microcapsule walls. The walls consist of a highly cross-linked polymer network, which entraps the material within. The permeability and size of the microcapsules, and the coordinating properties of the matrix can be tuned by selecting the type of wall-forming oligomer or monomer, type and quantity of porogenic (i.e., organic) solvent, agitation conditions, chain extenders, and other additives. The polyurea matrix was selected, because of its ability to ligate transition-metal salts, which was considered important for both efficient microencapsulation and subsequent retainment of the metal within the matrix when used as a catalyst.[20] It was also considered that the polyurea matrix would be relatively inert to chemical modification and give a physically robust material. In addition, the process facilitates a cost-effective method of production, which is an important consideration if the catalysts are to be utilized for industrial-scale manufacturing.

## 3. Catalyst Preparation

The method described by Ley to form the microcapsules involves the dispersion of a solution of an aromatic polyfunctional isocyanate and palladium acetate in dichloroethane into water containing a combination of industrial colloid stabilizers and surfactants.[20] The oil-in-water dispersion is obtained under medium shear stirring to give oil droplets in the 20–250-μm size range. Once the correct oil droplet size distribution is obtained, the polymerization is initiated by heating (**Figure 1**).[20] This causes some isocyanate groups at the oil–water interface to hydrolyze to the amine (via the unstable carbamic acid), which immediately reacts further intermolecularly with nonhydrolyzed isocyanate to form the urea-linked polymeric matrix (**Scheme 1**).[20] The resulting polyurea microcapsules are typically hard, porous, highly cross-linked spheres with a particle size average around 150 μm (**Figure 2a**). The beads are washed with water and organic solvents to remove stabilizers, loosely coordinated palladium, and any low-molecular-weight matrix material.

In addition to microencapsulation of Pd(II) salts, typically $Pd(OAc)_2$, Ley also reported the successful encapsulation of Pd(0) nanoparticles stabilized by tetraoctylammonium bromide.[20] Following solvent washing to remove the stabilizers, transmission-electron-microscopic (TEM) analysis of the microcapsules revealed the presence of palladium nanoparticles of 5 nm average diameter, suggesting that the nanoparticles were being stabilized by the polyurea matrix.

### 3.1. Microcapsule Morphology

Scanning- and transmission-electron-microscopic studies showed the interior of the spherical microcapsules to be made up of a uniform porous microstructure with no evidence for the core–shell morphology (**Figures 2b** and **2c**). The energy dispersive X-ray (EDX) pattern from SEM analysis of ultramicrotone cross sections of the microcapsules showed a homogeneous distribution of Pd throughout the cross-sectional area (**Figure 2d**). Analysis of

all X-rays coming off the microcapsule section showed evidence for Pd, Cl, N, O, and C, where Cl is derived from the solvent used in the preparation process and, as expected, shows a higher concentration in the center of the microcapsule.

### 3.2. Microcapsule Porosity

The porosity of the microcapsule is controlled—as in the case of other macro- and mesoporous organic polymers—by the composition of the organic phase (functionality of the isocyanate in this case) and, in particular, the ratio of porogenic solvent to aromatic isocyanate. Ley reported that the ratio of isocyanate to solvent was normally 40:60 (w/w), and the quantity of palladium acetate microencapsulated in dry microcapsules was 0.4 mmol/g as determined by inductively coupled plasma (ICP) analysis.[20] In the rest of this review, the microcapsule products will be described by the following shorthand: **metal loading** (mmol/g), **metal type**, **EnCat™**, **isocyanate in organic phase** (%). Thus, 0.4 Pd(II) EnCat™ 40 defines a polyurea-microencapsulated palladium(II) catalyst with an oxidation state of +2, where the organic phase had contained 40% isocyanate monomer.

The porosity of the 0.4 Pd(II) EnCat™ 40 microcapsules was determined in both the dry and solvent-wet states. In the dry state, the Brunauer–Emmett–Teller (BET) $N_2$ adsorption method gave a surface area of only 0.07 $m^2/g$ and an isotherm shape characteristic of a nonporous or macroporous material. Mercury intrusion porosimetry showed no evidence for accessible macropores in the dry resin.[26] Similar results were obtained for analogous microcapsules prepared with 30% polyfunctional isocyanate in the organic phase (0.4 Pd(II) EnCat™ 30).[26a] However, for a catalyst designed to work in solvents, the porosity of the solvent-swollen matrix is of more interest. An indication of how this porosity might change with solvent was obtained by measuring the percent gain in weight of a range of microencapsulated catalysts, including 0.4 Pd(II) EnCat™ 40, following immersion in various solvents at room temperature for over two hours (**Table 1**).[26a] As expected, polar aprotic solvents (e.g., DMA and DMF) and those able to disrupt intermolecular hydrogen-bonding interactions between polymer chains are the most efficient at swelling the polyurea matrix. It was also noted that reducing the isocyanate functionality of the matrix-forming oligomer produced an intrinsically more swellable matrix (Table 1, column 4). The reason for this is that the ability of a cross-linked polymer to swell in a solvent is inversely proportional to the length of polymer chain between cross-linked sites, which will therefore decrease as the monomer functionality increases.

The porosity of the polyurea matrix in the solvent-swollen state was investigated for Pd(II) EnCat™ 30 and Pd(II) EnCat™ 40 using chromatographic porosimetry.[27] This investigation was performed by passing standard solutions of polystyrene and alkylbenzenes through an HPLC column packed with a known mass of Pd(II) EnCat™, pre-swollen in THF, and recording the retention times. Averaged, normalized retention volumes per gram of Pd(II) EnCat™ for each analyte were used by PSS's POROCheck software program[28] to calculate the average pore volumes, surface areas, and pore diameters. The data in **Table 2**[26a] and **Figure 3**[26a] show that Pd(II) EnCat™ 40 has a significantly lower pore volume and diameter than Pd(II) EnCat™ 30. A consequence of this is that relatively low-molecular-weight molecules (>400 polystyrene equivalents) could be excluded from the pores in the Pd(II) EnCat™ 40 matrix, whereas molecules of molecular weight up to 1,000 polystyrene equivalents can gain access to the pores within the Pd EnCat™

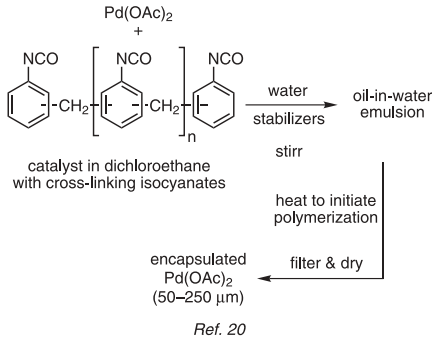
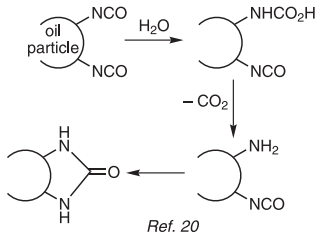



**Figure 1**. Interfacial Microencapsulation of Palladium in a Polymer Matrix.




**Scheme 1**. The Polyurea-Matrix-Forming Reaction That Occurs at the Oil–Water Interface.

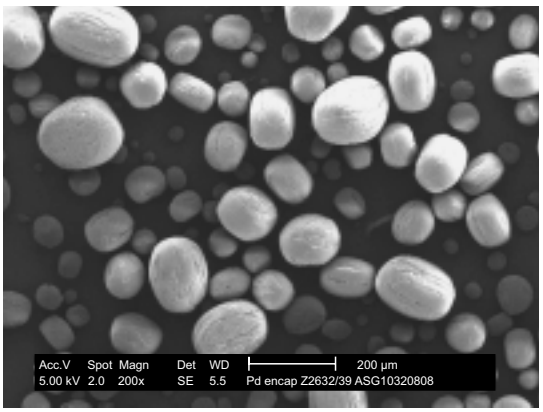



**Figure 2a**. Scanning Electron Microscope (SEM) Image of Microcapsules Containing $Pd(OAc)_2$.
(Photo courtesy of Avecia Ltd, and is reproduced with permission.)

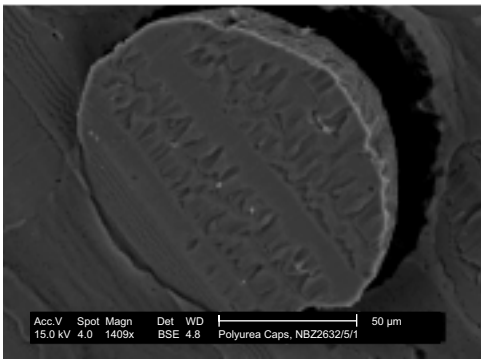



**Figure 2b**. SEM Image of the Interior of a $Pd(OAc)_2$-Containing Microcapsule.
(Photo courtesy of Avecia Ltd, and is reproduced with permission.)

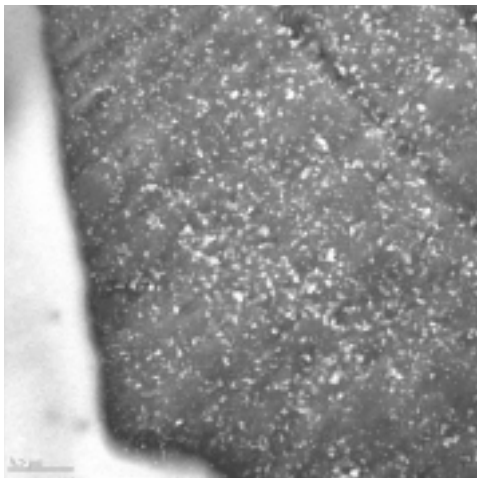


**Figure 2c**. Transmission Electron Microscope (TEM) Image of Ultramicrotone Cross Sections of $Pd(OAc)_2$-Containing Microcapsules. (Photo courtesy of Avecia Ltd, and is reproduced with permission.)

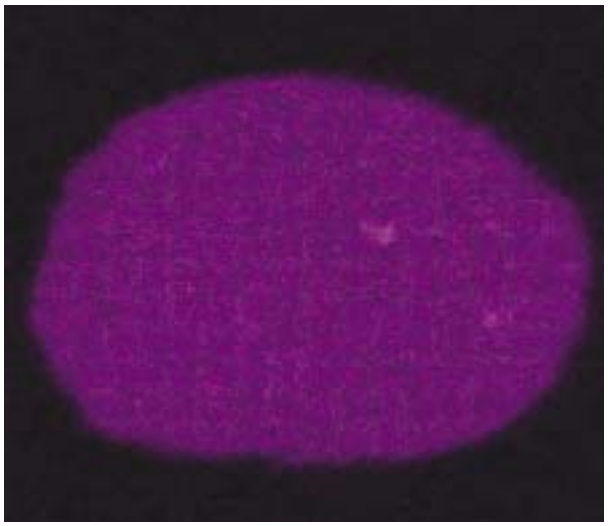


**Figure 2d**. Energy Dispersive X-ray (EDX) Pattern from SEM Analysis of Ultramicrotone Cross Sections of $Pd(OAc)_2$-Containing Microcapsules. (Photo courtesy of Avecia Ltd, and is reproduced with permission.)

**Table 1. Microcapsule Swelling Behavior as a Function of Solvent[a] and Matrix**

| | % Weight Gain | | | |
|---|---|---|---|---|
| Solvent | Pd(II) EnCat™ 40 | Pd(II) EnCat™ 30 | Pd(II) EnCat™ 20 | Reduced Cross-Linked Pd(II) EnCat™ 40[b] |
| PhMe | 0 | 30 | 30 | 0 |
| *i*-PrOH | 5 | 30 | 30 | 10 |
| EtOH | 10 | 30 | 30 | 20 |
| MeC(O)Me | 20 | 20 | 40 | 20 |
| THF | 10 | 60 | 40 | 10 |
| $MeC(O)NMe_2$ | 100 | 140 | 140 | 200 |
| $HC(O)NMe_2$ | 100 | 120 | 120 | 260 |

[a] The listed solvents are arranged in order of increasing polarity from top to bottom of column. [b] Half of the 2.7-functional isocyanate oligomer was replaced with a 2.0-functional isocyanate (2,4-toluene diisocyanate).

*Ref. 26a*

30 matrix. The higher porosity of the Pd(II) EnCat™ 30 matrix leads to improved access of reagents to the active metal centers, which results in higher yields and faster conversions.

### 3.3. Metal Leaching

A key feature of the polyurea encapsulation approach is the ability of the microcapsules to retain the palladium by virtue of the ligating functionality of the polymer. This was elegantly demonstrated by carrying out palladium leaching experiments in a range of solvents (**Table 3**).[26b] The results indicate that only in solvents capable of strongly swelling the matrix (Table 3, entries 1, 9, and 10) is there any significant metal leaching, while >99.8% of the metal remains within the microcapsule in all other solvents.

## 4. Catalytic Applications of Encapsulated Pd(II)

### 4.1. The Suzuki Reaction

Initial screening of the catalytic activity of 0.4 Pd(II) EnCat™ 40 was reported by Ley in the Suzuki-type cross-coupling of arylboronic acids with aryl bromides (**eq 1**).[20] ICP analysis of the crude products, following facile removal of the catalyst by filtration and evaporation of the solvent, detected palladium levels of about 13 ppm, which correspond to just 0.2% of the palladium originally in the microcapsules. Typically, for a homogeneous catalyst used at a similar equivalence, there would be several thousand ppm of palladium in the crude product. It was also reported that the catalyst was reused at least four times without significant loss of reactivity. A further benefit noted was that these reactions proceeded without the addition of phosphine ligands, which are both expensive and difficult to remove from the product.

Holmes, Ley, and co-workers recently evaluated a range of homogeneous tetrabutylammonium salts in order to develop protocols for carrying out Suzuki reactions using Pd(II) EnCat™ 40 under mild conditions with just stoichiometric quantities of base.[29] Typically, such reactions entail elevated temperatures (>90 °C) and the use of 2 to 4 equivalents of base. Initial investigations centered upon batch-type Suzuki reactions in toluene–methanol (9:1, v/v) in the presence of stoichiometric quantities of $(n\text{-Bu})_4NOAc$ or $(n\text{-Bu})_4NOH$ (1 M in MeOH), $(n\text{-Bu})_4NOMe$ (20% w/v in MeOH), or $(n\text{-Bu})_4F$ (1 M in THF). At 110 °C, and in the presence of Pd(II) EnCat™ 40, all four $(n\text{-Bu})_4NX$ salts were extremely effective at facilitating the cross-coupling of bromobenzene and *p*-tolylboronic acid, thereby giving rise to 4-methylbiphenyl in near-quantitative yields (**eq 2**).[29] At 40 °C, high coupling yields were obtained with $(n\text{-Bu})_4NOH$ and good yields with $(n\text{-Bu})_4NOMe$ and $(n\text{-Bu})_4F$. It was suggested that the higher coupling yields observed at 40 °C for $(n\text{-Bu})_4NX$ (X = OH, OMe, and F) relative to that seen with $(n\text{-Bu})_4NOAc$ may be attributed to the strongly nucleophilic nature of the hydroxide, methoxide, and fluoride anions, which facilitates the transmetalation process. These results demonstrate that the Suzuki cross-coupling reaction can be effected in organic solvents at low temperatures without the need for excess base.

A similar study was carried out with the more porous Pd(II) EnCat™ 30, 4-bromofluorobenzene and phenylboronic acid in isopropyl alcohol at 70 °C (**eq 3**).[26b] The results demonstrated that these batch reactions proceeded in high yields in less than 30 minutes in all cases except with $(n\text{-Bu})_4F$. Following removal of the catalyst by simple filtration and evaporation of the solvent, the crude products were found to contain just 20–50 ppm of palladium by ICP analysis. The high speed of these reactions and the low extent of catalyst leaching suggest that this system could be appropriate for a continuous-flow Suzuki application.

### 4.1.1. The Suzuki Reaction in Supercritical Carbon Dioxide

Supercritical carbon dioxide has a potential as an alternative solvent for organic synthesis,[30] and there has been considerable interest in performing hydrogenations[31] and C–C-bond-forming reactions[32] in this versatile solvent. Ley, Holmes, and co-workers further demonstrated the versatility of the microencapsulated catalyst in a series of Suzuki reactions, between *p*-tolylboronic acid and aryl halides in $scCO_2$, which proceeded in yields similar to those obtained in conventional organic solvents (**eq 4**).[33] Separation of the catalyst was achieved by simple filtration of the ethyl acetate solution into which the reaction mixture had been vented.

With a view to extending this technique to continuous-flow reactions, Lee et al. screened a series of tetrabutylammonium salts at 100 °C and 40 °C in the Pd(II) EnCat™ 40 mediated Suzuki coupling between bromobenzene and *p*-tolylboronic acid (**eq 5**).[29] At 100 °C and 3000 psi of $CO_2$, all four $(n\text{-Bu})_4NX$ salts gave 4-methylbiphenyl in near-quantitative yields. At 40 °C and 1400 psi, a good yield was obtained only with $(n\text{-Bu})_4NOMe$.

### 4.1.2. The Suzuki Reaction Under Continuous-Flow Conditions

Ley, Holmes, and co-workers were the first to achieve a continuous-flow Suzuki coupling over a Pd(II) EnCat™ 40 stationary phase.[29] In this feasibility study, a stock solution containing iodobenzene, *p*-tolylboronic acid, and $(n\text{-Bu})_4NX$ was passed through an HPLC column packed with Pd(II) EnCat™ 40 catalyst at 55 °C. The yield per pass through the column was determined by GC (**eq 6**).[29] These preliminary results were very encouraging in the case of $(n\text{-Bu})_4NOH$ and $(n\text{-Bu})_4NOMe$, giving rise to the biphenyl product in 70% and 85% yields, respectively, after just 3 passes. Even more impressive was the performance of $(n\text{-Bu})_4NOMe$ at 70 °C (entry 5), which gave a quantitative yield after one pass through the Pd(II) EnCat™ 40 stationary phase. In the case of the reactions with $(n\text{-Bu})_4NOAc$, $(n\text{-Bu})_4NF$, and $(n\text{-Bu})_4NOH$ at 55 °C, there was some phase separation of the reaction mixture, which probably explains the lower yields. It was suggested that the methanol liberated from $(n\text{-Bu})_4NOMe$ during the reaction solubilizes the other species, thus maintaining a homogeneous solution.

## 4.2. Carbonylation

The Cambridge researchers have also reported the formation of a range of substituted aryl esters in high yields by the Pd(II) EnCat™ 40 catalyzed addition of carbon monoxide to aryl iodides in *n*-butyl alcohol at 90 °C (**eq 7**).[33] The encapsulated catalyst was simply removed by filtration. Following solvent evaporation, the crude products contained approximately 79 ppm of Pd (w/w) corresponding to about 1% leaching of palladium from the microcapsules.

## 4.3. The Heck Coupling

Pd(II) EnCat™ 40 has been effectively utilized in a series of Heck couplings in conventional organic solvents (**eq 8**) and in $scCO_2$ (**eq 9**).[33] With $(n\text{-Bu})_4NOAc$, a series of unsaturated esters were produced in high yields (with the exception of the reaction with 4-bromoanisole) without the addition of phosphine ligands. It was noted that the yields were generally higher in $scCO_2$ even at a lower catalyst loading. Following removal of the catalyst and evaporation of the solvent, the crude products contained 60 ppm of palladium by ICP analysis.

Vickerstaffe et al. have recently reported the use of Pd(II) EnCat™ 40 in a Heck reaction that formed a key step in the first

**Table 2. THF-Wet-State Microcapsule Pore Dimensions by Chromatographic Porosimetry[a]**

| Property | Pd(II) EnCat™ 30 | Pd(II) EnCat™ 40 |
|---|---|---|
| Swollen bulk density (g/mL) | 0.330 | 0.469 |
| Swollen pore volume (mL/g) | 1.65 | 0.73 |
| Pore surface/pore volume ($m^2/cm^3$) | 1686.5 ± 20.3 | 2875.8 ± 46.2 |
| Average pore radius (nm) | 1.19 ± 0.01 | 0.70 ± 0.01 |

[a] Calculations use molecular statistical theory, and are based on a relationship between molecular weight and radius of gyration valid for polystyrene at molecular weights > 10,000 Daltons. Extrapolations below this molecular weight lead to unreliable absolute pore dimension data, but are valid for comparisons of similar materials using similar probe molecules.

*Ref. 26a*

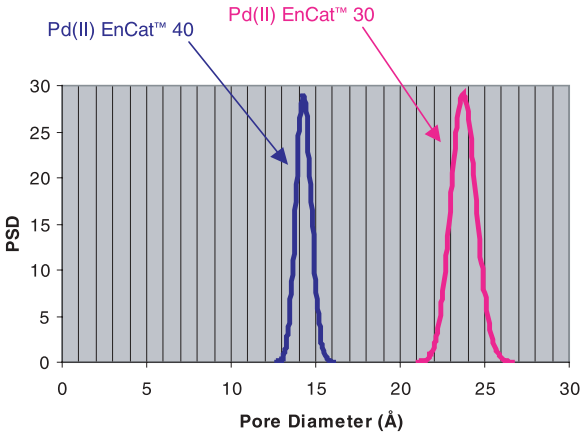


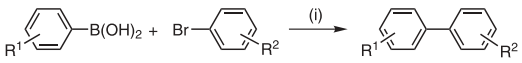

**Figure 3**. Pore Size Distribution (PSD) for Pd(II) EnCat™ 30 and Pd(II) EnCat™ 40 in the Tetrahydrofuran-Swollen State as Determined by Chromatographic Porosimetry. (Graph courtesy of Avecia Ltd, and is reproduced with permission.)

**Table 3. Palladium Leaching from Microcapsules[a]**

| | | 0.4 Pd(II) EnCat™ 40 | | 0.4 Pd(II) EnCat™ 30 | |
|---|---|---|---|---|---|
| Entry | Solvent | Pd (ppm) | % Pd Extracted[b] | Pd (ppm) | % Pd Extracted[b] |
| 1 | THF | 1 | 0.15 | 4 | 0.30 |
| 2 | Acetone | <1 | <0.15 | 1 | 0.08 |
| 3 | Ethanol | <1 | <0.15 | <1 | <0.08 |
| 4 | Acetonitrile | 1 | 0.15 | <1 | <0.08 |
| 5 | IPA | <1 | <0.15 | <1 | <0.08 |
| 6 | Toluene | <1 | <0.15 | <1 | <0.08 |
| 7 | Dioxane | 1 | 0.15 | <1 | <0.08 |
| 8 | Ethyl Acetate | <1 | <0.15 | <1 | <0.08 |
| 9 | DMF | 7 | 1.08 | 5 | 0.39 |
| 10 | DMA | 6 | 0.93 | 3 | 1.00 |

[a] The catalyst (0.3 g) was stirred and heated at 80 °C in the solvent (20 mL) for 2 days. The solid catalyst was then filtered off, and the palladium content of the filtrate determined by ICP analysis and expressed as ppm Pd in the solvent and as a percent of the total available Pd that was extracted by the solvent.
[b] Pd extracted as a percent of total palladium available.

*Ref. 26b*

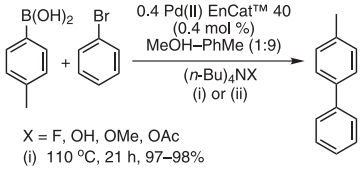



(i) 0.4 Pd(II) EnCat™ 40 (5 mol %), PhMe/$H_2O$/EtOH (4:2:1), $K_2CO_3$, 80 °C, 6–12 h
$R^1$ = H, 2-OMe, 4-OMe, 4-Ac
$R^2$ = 4-F, 2-OMe, 4-OMe, 4-$NO_2$

71–97%

*Ref. 20*

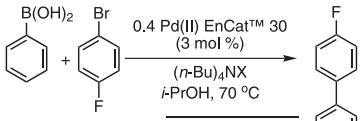
**eq 1**




X = F, OH, OMe, OAc
(i) 110 °C, 21 h, 97–98%
(ii) 40 °C, 60 h, 59–85%

*Ref. 29*

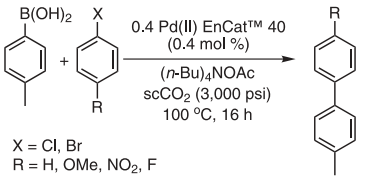
**eq 2**




| X | 0.5 h | 1.0 h |
|---|---|---|
| OAc | 84% | 84% |
| OH | 92% | 92% |
| OMe | 80% | 80% |
| F | 8% | 23% |

*Ref. 26b*

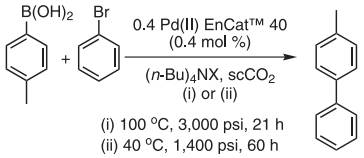
**eq 3**




X = Cl, Br
R = H, OMe, $NO_2$, F

*Ref. 33*

**eq 4**



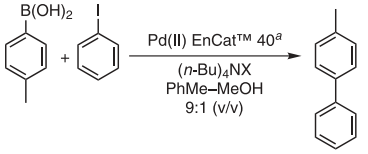

(i) 100 °C, 3,000 psi, 21 h
(ii) 40 °C, 1,400 psi, 60 h

| X | Yield (%) Method (i) | Yield (%) Method (ii) |
|---|---|---|
| OAc | 51 | — |
| OAc[a] | 96 | 38 |
| OH | 97 | 16 |
| OMe | 97 | 66 |
| F | 74 | <1 |

[a] A small amount of MeOH was used as additive.

*Ref. 29*

**eq 5**




| X | T, °C | % Yield per Pass[b] 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| OAc | 55 | 4.7 | 7.5 | 11 | 12 | 14 | 15 |
| OH | 55 | 3.1 | 13 | 70 | – | – | – |
| OMe | 55 | 12 | 48 | 85 | – | – | – |
| F | 55 | 36 | 40 | 55 | – | – | – |
| OMe | 70 | 100 | – | – | – | – | – |

[a] Used as a stationary phase in a continuous-flow Suzuki cross-coupling reaction: column 5 cm (l) × 4.5 mm (i.d.); flow rate 0.2 mL/min; residence time ca. 4 min. [b] Percent yield per pass through the HPLC column was determined by GC.

*Ref. 29*

**eq 6**

fully automated, unattended, multistep, and polymer-assisted solution-phase (PASP) synthesis of an array of histone deacetylase (HDAc) inhibitors. Despite the number of continuous steps, they were able to obtain 34 out of the 36 targeted compounds in reasonable yields and purities.[34] The Heck olefination of an iodophenyl sulfonamide with acrylic acid was investigated using the immobilized palladium catalysts Pd(II) EnCat™ 40 and Fibrecat™ 1001[35] as a way to facilitate product workup (**eq 10**).[34] Using a ReactArray SK233 automated reaction sampling system, it was demonstrated that the competing dehalogenation pathway was minimized using Pd(II) EnCat™ 40 as the source of palladium with tributylamine as base, and that the desired product was obtained in 80% yield after 13.3 h versus a 60% yield with Fibrecat™ 1001—a polyethylene-supported, phosphine-ligand-based palladium catalyst.[11]

### 4.4. The Intramolecular Heck Coupling

Smith and collaborators have reported that Pd(II) EnCat™ 40 can be effectively applied in intramolecular olefination reactions in acetonitrile or DMF (**eq 11**).[36] Unlike $Pd(PPh_3)_4$, the encapsulated catalyst does not produce triphenylphosphine oxide as a byproduct, and only a slight palladium contamination of the products is observed. Faster reactions are usually obtained with DMF, presumably because DMF allows some leaching of palladium from Pd(II) EnCat™; the encapsulated catalyst in this case probably acts as a convenient slow-release reservoir of highly active nanoparticulate Pd(0) species.

### 4.5. The Stille Coupling

The utility of Pd(II) EnCat™ 40 was further demonstrated in a series of Stille couplings in conventional organic solvents and in $scCO_2$ (**eq 12**).[33] It was noted that the yields in $scCO_2$ were lower than those in isopropyl alcohol–toluene, although less catalyst was used in $scCO_2$. The feasibility of reusing the recovered catalyst was also demonstrated by performing a series of sequential Stille reactions of phenyltrimethylstannane with 4-nitrobromobenzene. In all cases, the reactions proceeded to completion giving a near-quantitative yield (97–99%) of the coupled product. A progressive increase in reaction time in successive runs was also observed, indicating that some of the more accessible metal may have been removed in the preceding reaction or after washing with solvent following recovery of the catalyst.[33]

### 4.6. Parallel Synthesis of Chemical Libraries

The Suzuki coupling of boronic acids or boronates with aryl halides is a powerful diversity-generating reaction. Microwave heating dramatically improves reaction times and conversions and, with diverse substrates, provides an opportunity for a more general reactivity.[37]

Wang and Sauer have described the use of microwave heating in Suzuki cross-couplings that utilize FibreCat™ 1001 (**eq 13**).[38] Good yields and purities were obtained by using an excess of the boronic acid and solid-phase extraction with a silica-supported carbonate base during workup. The use of Pd(II) EnCat™ 40 in a microwave-promoted synthesis of a biaryl library from a diverse set of boronic acids and aryl halides has been reported (**eq 14**).[36,39] A Personal Chemistry Synthesizer microwave reactor was utilized together with an experimental design strategy that optimized conditions including solvent, temperature, base, stoichiometry, and time against substrate reactivity in order to generate robust general reaction conditions. The base, tetra(*n*-butyl)ammonium acetate, was dispensed in acetonitrile prior to reaction. After cooling, the microencapsulated catalyst was

filtered prior to purification. Alternatively, the reaction mixture was applied directly to disposable chromatography cartridges and purified, thus separating the catalyst at the same time. The library was constructed by reacting 19 aryl halides with 12 boronic acids to produce a set of 157 pure biaryl products (68% success rate).

## 5. Catalytic Applications of Encapsulated Palladium(0)

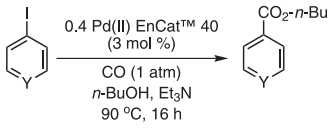
### 5.1. Hydrogenation

The reduction of Pd(II) EnCat™ 40 with hydrogen produces Pd(0) EnCat™ 40, which is an effective catalyst for the selective hydrogenation of unsaturated bonds in alkenes, alkynes, imines, and nitro groups (**eq 15**).[40] Recovery of the catalyst is simple compared to that of palladium-on-carbon, levels of metal contamination in the crude products are extremely low, and the catalyst can be readily recycled. All of the initial hydrogenations reported were carried out with Pd(0) EnCat™ 40 pre-reduced under hydrogen (50 bar) for two days. It was found that this pre-reduction of Pd(II) EnCat™ 40 was necessary for high activity and reduced reaction times. The hydrogenations were carried out under a hydrogen atmosphere either in an autoclave or maintained by a hydrogen-filled balloon.

Simple alkenes, alkynes, and aryl nitro groups were reduced at room temperature under an atmosphere of hydrogen (inflated balloon) with near-quantitative conversions as determined by GC or LCMS. Using cyclohexene as a test substrate, it was demonstrated that the catalyst could be recycled 20 times without any significant loss of activity. The reduction of electron-deficient styrenes was sluggish at room temperature and required slightly elevated temperatures (60 °C) to yield the reduced products. Reduction of *trans*-*N*-phenylbenzylidene, on the other hand, required the use of high pressure (50 bar). Interestingly, potentially labile groups such as alkyl epoxides, aryl halides, and benzyloxy groups remained unaffected even after being subjected to high pressures (up to 50 bar) and extended reaction times. However, the benzyloxycarbonyl group in *N*-Cbz-*N*-methylallylamine was cleaved under high pressure (50 bar), whereas the same group remained intact when the same reaction was performed under an atmosphere of hydrogen (maintained by a hydrogen balloon), which gave rise to the reduced product in 93% isolated yield. All of the crude products from the hydrogenations contained less than 10 ppm of palladium, as determined by ICP analysis, which corresponds to <0.025% of the original metal being lost from the encapsulated catalyst. These results demonstrate that, although less reactive than Pd/C, Pd(0) EnCat™ 40 allows the selective reduction of double bonds to be carried out in the presence of sensitive functionalities. When coupled with its ease of handling, facile removal from reaction mixtures, and apparent reduced pyrophoric tendency, this selectivity makes Pd(0) EnCat™ 40 an attractive choice for large-scale operations.

### 5.2. Transfer Hydrogenation

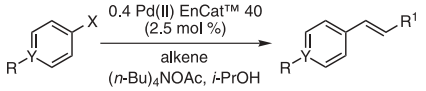
While the hydrogenation of Pd(II) EnCat™ 40 did not produce an active catalyst for transfer hydrogenation reactions,[41] the formic acid reduction of the microencapsulated Pd(II) resulted in a highly effective transfer-hydrogenation catalyst.[42] An examination of high-resolution TEM images of Pd(0) EnCat™, produced by reduction with hydrogen or with formic acid, confirmed the hypothesis that polyurea-coordinated $Pd(OAc)_2$ undergoes anionic ligand exchange with formate to form a palladium diformate complex (**Scheme 2**).[41] This complex is known to undergo decarboxylation followed by loss of molecular hydrogen to form Pd(0), which is deposited as fine nanoparticles within the




Y = C–R; R = Me, OMe, COMe; 89–99%
Y = N; 93%

*Ref. 33*

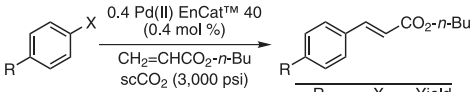
**eq 7**




| Y | R | X | $R^1$ | Yield |
|---|---|---|---|---|
| C | $NO_2$ | Br | $CO_2$(*n*-Bu) | 91% |
| C | $NO_2$ | Br | Ph | 93% |
| N | – | I | $CO_2$(*n*-Bu) | 98% |
| C | OMe | Br | $CO_2$(*n*-Bu) | 25% |

*Ref. 33*

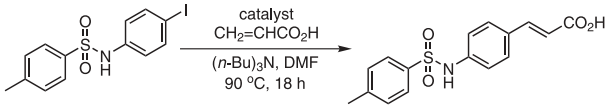
**eq 8**




| R | X | Yield |
|---|---|---|
| H | Br | 99% |
| OMe | Br | 99% |
| F | Br | 75% |
| $NO_2$ | Br | 95% |
| $NO_2$ | Cl | 58% |

*Ref. 33*

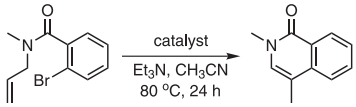
**eq 9**




0.4 Pd(II) EnCat™ 40 (0.4 mol %), 80%
Fibrecat™ 1001, 60%

*Ref. 34*

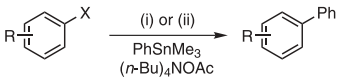
**eq 10**




0.4 Pd(II) EnCat™ 40 (5 mol %), 50%
(DMF, 120 °C, 5 h; 80%)
or
0.4 Pd(II) EnCat™ 30 (5 mol %), 50%

*Ref. 36*

**eq 11**

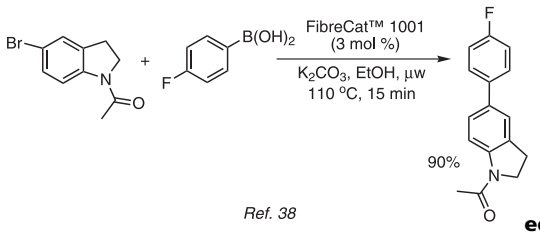



(i) 0.4 Pd(II) EnCat™ 40 (2.5 mol %),
PhMe–*i*-PrOH (1:1), 90 °C
(ii) 0.4 Pd(II) EnCat™ 40 (0.4 mol %),
$scCO_2$ (3,000 psi), 100 °C, 16 h

| R | X | Yield (i) | Yield (ii) |
|---|---|---|---|
| H | Br | – | 50% |
| 2-OMe | Br | 74% | – |
| 4-OMe | Br | 88% | 45% |
| 4-F | Br | 82% | – |
| 4-$NO_2$ | Br | 99% | >34% |
| 4-$NO_2$ | Cl | – | 50% |

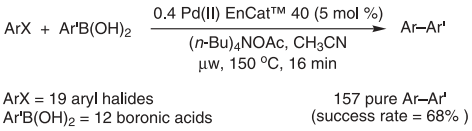
*Ref. 33*

**eq 12**



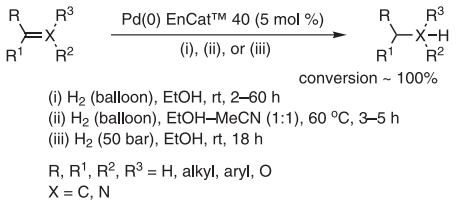

*Ref. 38*

**eq 13**



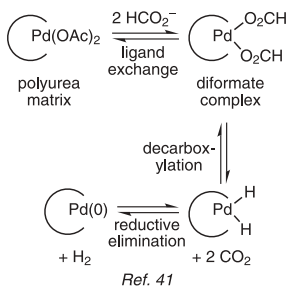

*Ref. 36,39*

**eq 14**



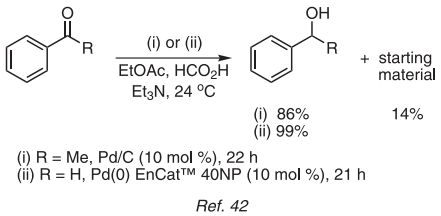

*Ref. 40*

**eq 15**



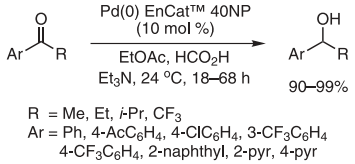

*Ref. 41*

**Scheme 2**. Formation of Nanoparticulate Pd(0) via Ligand Exchange with the Formate Anion.




*Ref. 42*

**eq 16**




*Ref. 42*

**eq 17**

polyurea matrix.[41] It was anticipated, that following reduction of the homogeneous palladium(II), the polyurea matrix would prevent agglomeration of the palladium(0) nanoparticles.

In the sample prepared by reduction of Pd(II) EnCat™ 40 with hydrogen, the majority of the Pd(0) particles were found to be larger than 5 nm in diameter. In contrast, images of Pd(0) particles produced by reduction with formic acid revealed that most of the particles have a diameter of ≤2 nm, and provided evidence for highly ordered areas corresponding to the preferred cubic, close-packed palladium cell structure.[41]

Ley and co-workers first established the efficiency and stability of this new nanoparticulate Pd(0) catalyst, Pd(0) EnCat™ 40NP, by examining the reduction of acetophenone (10 mol % Pd(0) EnCat™ 40NP, 200 μL EtOAc, 0.8 mmol $HCO_2H$, 0.8 mmol $NEt_3$, 0.016 mmol PhC(=O)Me, 24 °C).[42] The reduction proceeded to completion with excellent isolated yields (96–99%) through five successive recycle runs and, importantly, there was no evidence for compounds formed from over-reduction of the aromatic ring or cleavage of the hydroxyl group.

The superior catalytic properties of Pd(0) EnCat™ 40NP, as compared to those of 10% Pd/C, were demonstrated by carrying out the reduction of propiophenone under identical conditions: 10% Pd/C facilitated only an 86% conversion to the benzyl alcohol product (**eq 16**).[42]

It has been noted that the metal center within the Pd(0) EnCat™ 40NP catalyst is more electron-rich than Pd/C, which may account for the higher catalytic activity. It has been further suggested that the small size of the palladium nanoparticles may also have a profound effect.[41,42] The scope of this new catalyst system was established by carrying out a wide range of aryl ketone transfer reductions. In all cases, the reactions reached completion within 18 to 68 hours and led to very high yields of the secondary alcohol products (**eq 17**).[42]

### 5.3. Transfer Hydrogenation in Parallel Synthesis

More recently, nanoparticulate Pd(0) EnCat™ NP has been used as an alternative to Pd/C in automated, parallel transfer hydrogenations to prepare a library of biaryl alcohols of interest as herbicide intermediates.[36,43] This catalyst system is attractive in parallel synthesis, where chemists prefer not to use gaseous hydrogenation and potentially pyrophoric reagents. The higher activity, ease of catalyst removal by simple filtration, and the reduced risk from ignition of solvent–air mixtures should make this the catalyst system of choice in parallel transfer hydrogenations.

Pd(0) EnCat™ 40NP can be readily separated from parallel-synthesis reaction mixtures using polypropylene reaction tubes. The tubes are sintered at the bottom, allowing gravity or vacuum-assisted filtration from 48-position reactor blocks via outlet tubes with a universal locking mechanism. As part of an experiment to further explore the scope of the reduction of aryl ketones, 96 diverse ketones were reacted in parallel with Pd(0) EnCat™ 40NP under standard transfer-hydrogenation conditions [Pd(0) EnCat™ 40NP (10 mol %), EtOAc, $Et_3N$, $HCO_2H$, 24 °C, 48 h].[36,43] After filtration and evaporation, the residues in dichloromethane were treated with water and filtered through a phase-separation plate. In many cases, high conversions (79–100%) were observed, leading to pure products, the purities of which were established by GC and NMR. Very hindered or electron-rich aromatic ketones were found to be unreactive or slower to reduce. Biaryl ketones, such as benzophenone, showed significant amounts of over-reduction to the corresponding methylene compounds. Aromatic halides (except fluorine) were also rapidly reduced; for example, 1-pentoyl-2,4-dichlorobenzene gave pure α-pentyl

benzyl alcohol (100% yield). This provides a very mild method for dechlorination of aromatic substrates. 2-Acylpyridine was reduced to the corresponding alcohol (79% yield), whereas 3-acylpyridine was reduced to the corresponding tetrahydropyridine (59% yield). Reactions with electron-rich or sterically hindered ketones were much more sluggish. Optimization experiments of catalyst loading and reagent stoichiometry indicated that efficient conversions could be obtained with acetophenone down to 2 mol % Pd(0) EnCat™ 40NP and only two equivalents of formic acid and triethylamine. A comparison of Pd(0) EnCat™ 40NP with the more porous Pd(0) EnCat™ 30NP using standard conditions, showed the latter to be far more effective with the least reactive substrates (**eq 18**).[36]

### 5.4. Reduction of the Aryl Nitro Group

Pd(0) EnCat™ 40NP has been employed in the reductive cyclization of various Leimgruber–Batcho-derived enamines to form the corresponding indoles (**Scheme 3**).[44] Hydrogenation of the aryl nitro group was carried out under transfer-hydrogenation conditions to give the indole in high yield. The catalyst was recycled without noticeable loss in activity, and the reaction was accelerated by microwave irradiation at 120 °C. Thus, the combination of microwave-accelerated enamine formation and the use of a recyclable, easily removed catalyst for the reductive cyclization in the Leimgruber–Batcho reaction provides an industrially attractive route to indoles.

### 5.5. Reductive Ring Opening of Epoxides

The reductive ring opening of epoxides by hydrogenolysis in the presence of Pd(0) EnCat™ 40NP has been investigated.[41] For example, the hydrogenolysis of *trans*-stilbene oxide gave the alcohol in 99% isolated yield after 5 h. Over-reduction of the alcoholic C–O bond was not observed at a detectable level even after prolonged reaction times. This illustrates the clear advantage of Pd(0) EnCat™ 40NP over Pd/C in terms of chemoselectivity. Under identical conditions, 10% Pd/C gave the desired secondary alcohol in 80% yield from *trans*-stilbene oxide, and in only 48% yield from methylstyrene oxide.[26] In these Pd(0) EnCat™ 40NP reductions, the catalyst was recovered by simple filtration and reused without loss of activity. In the case of *trans*-stilbene oxide, the catalyst was recycled through 10 successive hydrogenolysis reactions and, in each case, gave high isolated yields (96–99%) of the corresponding benzylic alcohol. Moreover, the level of palladium in the reaction medium following filtration of the catalyst was below the detection limit (5 ppm) of ICP analysis.[41]

A range of other benzylic epoxides were also subjected to the same hydrogenolysis conditions, and good-to-excellent yields (82–99%) of the homobenzylic alcohols were consistently obtained. In each case, the epoxides were opened regioselectively at the benzylic carbon. The stereoselectivity of the ring opening was investigated by using enantiomerically pure *trans*-methylstyrene oxide, which was reduced with complete retention of configuration at the homobenzylic carbon atom (**eq 19**).[41]

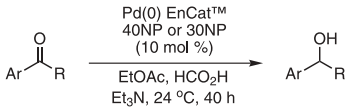
We have demonstrated that methyl styrene oxide undergoes hydrogenolysis faster with the more porous Pd(0) EnCat™ 30NP than with Pd(0) EnCat™ 40NP. A near-quantitative conversion into the anticipated product occurred in less than 30 minutes.[26b] Furthermore, the catalyst (EnCat™ 30NP or 40NP) was readily recovered and recycled and, following catalyst removal and solvent evaporation, the product contained less than 5 ppm of palladium by ICP analysis.

#### 5.5.1. Reductive Ring Opening of α,β-Epoxy Ketones

The β-hydroxy carbonyl functionality is an important structural motif, which often appears in natural products and can generally be installed by an aldol reaction. This is not always convenient, however, and reductive cleavage of α,β-epoxy ketones is an important alternative. Ley's group demonstrated that α,β-epoxy ketones undergo reductive cleavage in the presence of Pd(0) EnCat™ 40NP to give the corresponding β-hydroxy ketones in good yields (**eq 20**).[41] NMR analysis indicated that the main side product was the diketone.

#### 5.5.2. Reductive Ring Opening of Terminal Epoxides

Due to recent advances in the area of catalytic epoxidation of terminal olefins,[45] the regioselective reduction of terminal epoxides is a particularly attractive route to substituted alcohols. Unfortunately, the reduction of (2,3-epoxypropyl)benzene with Pd(0) EnCat™ 40NP under transfer-hydrogenation conditions was very slow. But, encouragingly, a good yield (85%) of the

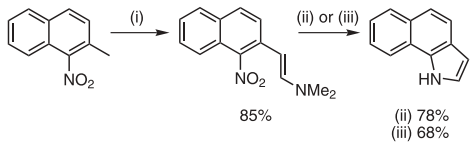



| Ar | R | Ar,R | Conversion[a] with 40NP | Conversion[a] with 30NP |
|---|---|---|---|---|
| 2-MeOC$_6$H$_4$ | Me | — | 4% | 13% |
| 3-MeOC$_6$H$_4$ | Me | — | 50% | 75% |
| 4-MeOC$_6$H$_4$ | Me | — | 28% | 54% |
| Ph | Cy | — | 55% | 93% |
| 1,3-benzodioxol-5-yl | Me | — | 10% | 29% |
| — | — | 1-indanone | 33% | 60% |
| — | — | 7-MeO-1-tetralone | <5% | 20% |
| — | — | 1-benzosuberone | 18% | 22% |

[a] Determined by GC or NMR.

*Ref. 36*

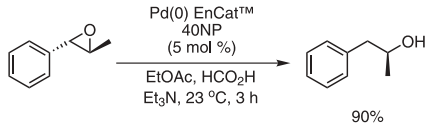
**eq 18**




(i) CuI or Yb(OTf)$_3$, DMF, μw, 180 °C, 4.5 h
(ii) Pd(0) EnCat™ 40NP (6 mol %), EtOAc, HCO$_2$H
Et$_3$N, 24 °C, 24 h
(iii) Pd(0) EnCat™ 40NP (6 mol %), EtOAc, HCO$_2$H
Et$_3$N, μw, 120 °C, 2 h

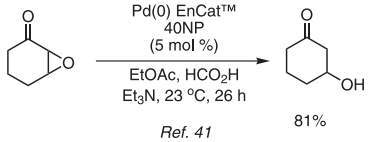
*Ref. 44*

**Scheme 3**. Leimgruber–Batcho Indole Synthesis.




*Ref. 41*

**eq 19**




*Ref. 41*

**eq 20**

secondary alcohol was obtained under conventional hydrogenation conditions [Pd(0) EnCat™ 40NP (5 mol %), MeOH, $H_2$ (40 atm), 23 °C, 19 h].[41]

## 6. Conclusions and Outlook

It is hoped that the above selected examples have demonstrated that polyurea-microencapsulated homogeneous catalysts offer advantages to the synthetic organic chemist both for laboratory-scale use and in manufacturing. The outlook for this field is exciting, with the potential to microencapsulate a range of homogeneous metal catalysts and ligands in tailored matrix materials.

## 7. Acknowledgments

This technology would not have been developed without initial funding from Syngenta for the original project at Cambridge University and the generous continuing support of the Engineering and Physical Sciences Research Council (EPSRC) and Avecia Ltd. The authors would particularly like to acknowledge the contributions of Drs. Chandra Ramarao, David Tapolczay, Ian McConvey, and Ian Shirley.

## 8. References and Notes

(§) Dedicated to Professor Steven V. Ley, CBE, FRS, on the occasion of his 60th birthday.

(†) Author to whom correspondence should be addressed. Email: david.pears@reaxa.com.

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## About the Authors

**David A. Pears** was born in St. Albans, England. He was raised in Harpenden and entered Southampton University in 1979, graduating with a B.Sc. (Honours) in 1982. He then joined Professor J. F. Stoddart's group at Sheffield University to carry out research on chiral crown ethers as enantioselective catalysts, and graduated with a Ph.D. in 1985. He joined ICI's New Science Group in the same year to work on the synthesis of novel-effect monomers for use in high-performance surface coatings. In 1990, he transferred to Holland to lead a research team within ICI's NeoResins business in developing water-based, UV rapid-cure coating systems. In 1993, he returned to the U.K. to work as Research Group Leader with Zeneca and, in 1998, was made Business Research Associate. In the same year, he joined Avecia as a group leader within its Core Polymer Group. He has published over 70 patents and scientific papers. David currently works within Avecia's Pharmaceuticals business in Manchester, England. In 2004, he was awarded the U.K.'s Chemical Industries Association "Innovation of the Year" award for the development of the Pd EnCat™ catalyst technology in collaboration with Professor Steven Ley and scientists at AstraZeneca and Syngenta.

**Stephen C. Smith** was born in Windsor, England. He studied chemistry at Imperial College, London, where he was awarded a B.Sc. degree in 1988. This was followed by a Ph.D. with Professor Steven Ley, CBE (Commander of the Order of the British Empire) at Imperial College, which was earned for work on the synthesis of the potent insect-antifeedant azadirachtin. In 1991, Steve moved to the University of California at Berkeley as a NATO fellow to conduct postdoctoral research with Professor Clayton Heathcock on the synthesis of the cytotoxic bis-steroidal cephalostatins. He returned to the U.K. to join what was then ICI Plant Protection at Jealott's Hill, Bracknell, at the end of 1992. This then became Zeneca Agrochemicals. Steve spent three years as a team leader in the Herbicide Chemistry group, working on a number of hit-to-lead and optimization projects, followed by two years on secondment in the Process Technology Department at Huddersfield in the U.K. Here, he led a team developing the first stages in a process to manufacture the active ingredient in the herbicide sulfosate. Steve returned to Jealott's Hill to work on new leads in insecticide chemistry and, in 1999, moved into his current role as Head of the Syngenta Chemical Technology Group. This encompasses combinatorial chemistry, robotic synthesis, and new synthetic technologies such as microwave chemistry, solid-phase synthesis, supported reagents, and catalysis. He is an author on over 50 scientific papers and patents. Steve led the original microencapsulated-catalyst joint collaborative project with Professor Steven Ley from 1999 to 2002. The project team (Syngenta, Avecia, AstraZeneca, and Cambridge University) received the Institute of Applied Catalysis (iAc) Innovation Award in 2004.

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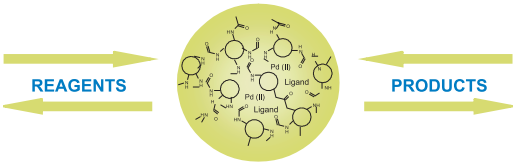
**Pd EnCat™** addresses these issues by using microencapsulation technology to immobilize the palladium, optionally with activating ligands, within a highly cross-linked polyurea matrix. The catalytic activity of palladium is accessed through the porous matrix, thereby leaving the palladium captured within it.

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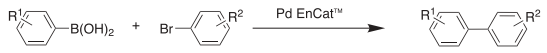
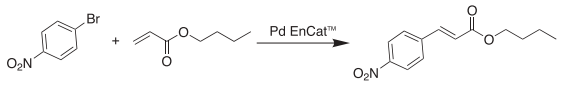
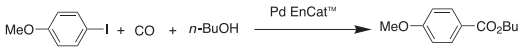
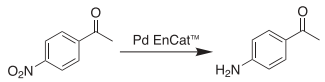
| | |
|---|---|
| Suzuki Coupling |  |
| Heck Reaction |  |
| Carbonylation |  |
| Transfer Hydrogenation |  |

**References:** (1) Yu, J.-Q. et al. *Chem Commun.* **2003**, 678. (2) Bremeyer, N. et al. *Synlett* **2002**, 1843. (3) Ley, S. V. et al. *Chem Commun.* **2002**, 1134. (4) Chandrashekar, R. et al. *Chem Commun.* **2002**, 1132. (5) Vickerstaffe, E. et al. *Org. Biomol. Chem.* **2003**, *1*, 2419. (6) Ley, S. V. et al. *Org. Lett.* **2003**, *5*, 4665.

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

| Cat No. | Name | Matrix Content (%) | %Pd (mmol/g) | P (mmol/g) | Ligand | Units | | |
|---|---|---|---|---|---|---|---|---|
| **64,472-2** | Pd EnCat™ 40 | 40 | 3.9–4.6 (0.4) | N/A | N/A | 1 g | 10 g | 100 g |
| **64,471-4** | Pd EnCat™ 30 | 30 | 3.9–4.6 (0.4) | N/A | N/A | 1 g | 10 g | 100 g |
| **64,470-6** | Pd EnCat™ TPP30 | 30 | 3.9–4.6 (0.4) | 0.26–0.35 | $Ph_3P$ | 1 g | 10 g | 100 g |
| **64,469-2** | Pd EnCat™ TOTP30 | 30 | 3.9–4.6 (0.4) | 0.15–0.20 | $(o\text{-toyl})_3P$ | 1 g | 10 g | 100 g |
| **65,366-7** | Pd EnCat™ 30NP, Wet | 30 | 3.7–4.6 (0.4) | N/A | N/A | 1 g | 10 g | 100 g |

*(45% water, unit weight excludes water)*

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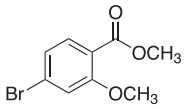
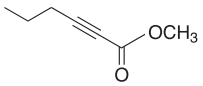
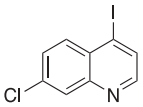


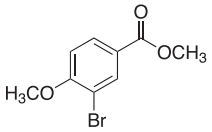
**Methyl 2-hexynoate, puriss., 98%**
**65,298-9** 5 g, 25 g



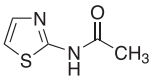
**7-Chloro-4-iodoquinoline, purum, 97%**
**65,290-3** 1 g, 10 g



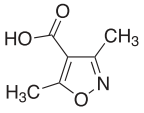
**Methyl 3-bromo-4-methoxybenzoate, puriss., 98%**
**65,283-0** 1 g, 10 g



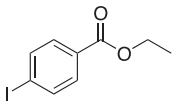
**2-Acetamidothiazole, 98%**
**64,838-8** 5 g



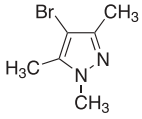
**3,5-Dimethylisoxazole-4-carboxylic acid, 98%**
**63,765-3** 1 g, 5 g



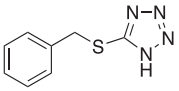
**Ethyl 4-iodobenzoate, 98%**
**66952** 10 g



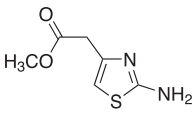
**4-Bromo-1,3,5-trimethylpyrazole, puriss., 98%**
**65,294-6** 1 g, 5 g



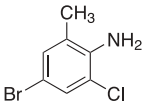
**5-(Benzylthio)-1*H*-tetrazole, ~0.25 M solution in acetonitrile**
**87757** 100 mL, 500 mL



**Methyl (2-amino-4-thiazolyl)acetate, puriss., 98%**
**65,302-0** 1 g, 5 g



**4-Bromo-2-chloro-6-methylaniline, 98%**
**64,875-2** 5 g, 25 g



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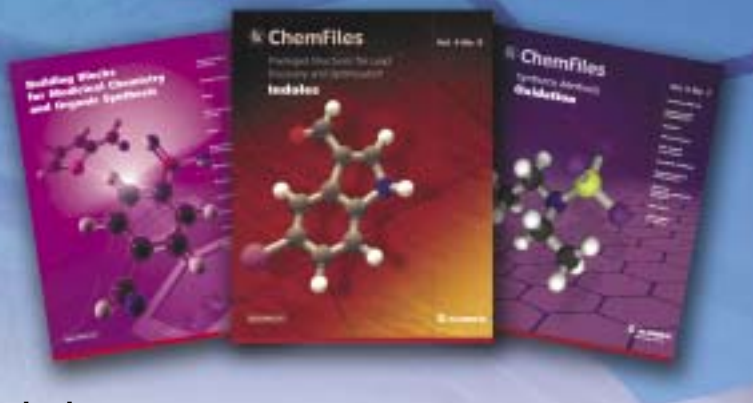


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|---|
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|---|---|
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Anti-climb.

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| 100 | 24/40 | 24/40 | **Z55,758-7** |
| 250 | 24/40 | 14/20 | **Z55,759-5** |
| 250 | 24/40 | 24/40 | **Z55,760-9** |
| 100 | 29/32 | 14/20 | **Z55,761-7** |
| 100 | 29/32 | 24/40 | **Z55,762-5** |
| 250 | 29/32 | 14/20 | **Z55,763-3** |
| 250 | 29/32 | 24/40 | **Z55,764-1** |

## Vacuum-Filtration Adapter

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| ⅀Joint | Flange I.D. (mm) | Cat. No. |
|---|---|---|
| 14/20 | 23 | **Z55,639-4** |
| 19/22 | 23 | **Z55,640-8** |
| 24/40 | 31 | **Z55,641-6** |
| 24/40 | 38 | **Z55,642-4** |
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| 29/42 | 38 | **Z55,644-0** |

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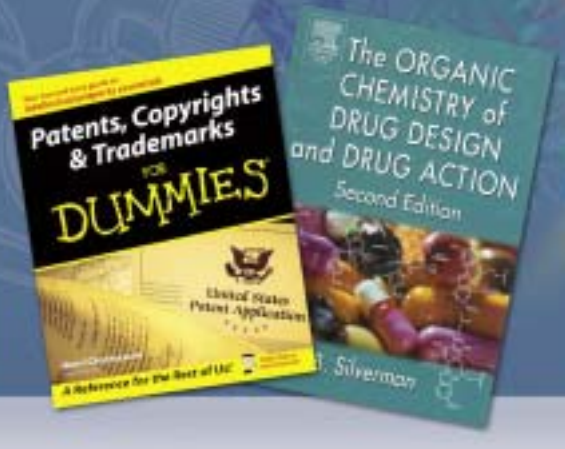


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*J. J. Li, Ed., Wiley, 2004, 558pp. Hardcover.* The chemistry of heterocyclic compounds and methods for their synthesis form the bedrock of modern medicinal, chemical, and pharmaceutical research. The primary topics include three- and four-membered heterocycles; five-membered heterocycles including indoles, furans, thiophenes, and oxazoles; six-membered heterocycles including quinolines, isoquinolines, and pyrimidines; and other heterocycles. Each name reaction is summarized in seven sections: description, historical perspective, mechanism, variations and improvements, synthetic utility, experimental, and references.

**Z70,312-5**

### Protecting Groups, 3rd Edition

*P J. Kocienski, Thieme Publishers, 2004, 679pp. Softcover.* Provides a concise and understandable presentation of modern protecting group methods. The introductory chapter provides a sophisticated overview of the application of protecting groups in contemporary syntheses. At the heart of the book are seven chapters, which deal authoritatively and thoroughly with the protection of the various core functional groups, from carbonyl to amino. The final chapter presents an insight into the realities of synthetic practice and twenty-five problems for people who love to understand chemistry.

**Z55,155-4**

## DRUG DISCOVERY TITLES

### The Organic Chemistry of Drug Design and Drug Action, 2nd Edition

*R. B. Silverman, Academic Press, 2004, 617pp. Hardcover.* Standard medicinal chemistry courses and texts are organized by classes of drugs with an emphasis on descriptions of their biological and pharmacological effects. This book represents a new approach based on physical organic chemical principles and reaction mechanisms that rationalize drug action and allow the reader to extrapolate to many related classes of drug molecules. The second edition reflects the significant changes in the drug industry over the past decade, and now includes color illustrations, chapter problems, and other elements that make concepts easier to understand.

**Z70,239-0**

### Chirality in Drug Design and Development

*I. K. Reddy and R. Mehvar, Eds., Marcel Dekker, 2004, 444pp. Hardcover.* Covers every essential element in the development of chiral products, and provides a solid overview of the formulation, biopharmaceutical characteristics, and regulatory issues impacting the production of these pharmaceuticals. Supports researchers as they critically evaluate the pharmacodynamic, pharmacokinetic, and toxicological characteristics of specific enantiomers and chiral drug compounds.

**Z70,245-5**

## ANALYTICAL CHEMISTRY TITLES

### Analytical Method Validation and Instrument Performance Verification

*C. C. Chan et al., Eds., Wiley, 2004, 320pp. Hardcover.* Full of practical tips on validation techniques and detailed discussions of instrument performance verification, this guide represents a one-stop reference for today's regulatory environment. Each chapter includes general requirements, strategies and steps taken to fulfill these conditions, and a discussion of practical problems and their solutions. Coverage includes: method validation of potency, related substances, and dissolution testing; validation for pharmaceutical excipients, heavy metals, and bioanalysis; performance verification for common analytical instruments including HPLC, UV-Vis spectrophotometers, and pH meters; LCMS system calibration; proper environmental chamber qualification; and entire qualification process for computer equipment, hardware, and software.

**Z70,199-8**

### NMR Spectroscopy: Data Acquisition, 2nd Edition

*C. Schorn and B. Taylor, Wiley, 2004, 380pp. Hardcover with CD-ROM.* This key to correct structure analysis is now in its second edition. The result is a volume encouraging beginners to use high-resolution NMR, while prompting experts to evaluate new experiments using the easily manageable Bruker simulation program 1D and 2D WIN-NMR of the accompanying CD-ROM. Newcomers may come to understand basic data acquisition procedures, modular pulse sequence units, and complete sequences in NMR spectroscopy.

**Z70,309-5**

## MATERIALS SCIENCE TITLES

### Nanoparticles: From Theory to Application

*G. Schmid, Ed., Wiley, 2004, 444pp. Hardcover.* This is an introduction to the science of nanoparticles, from fundamental principles to their use in novel applications. As a basis for understanding nanoparticle behavior, the book outlines the principles of quantum-size behavior, nanoparticles architecture, formation of semiconductor and metal nanoparticles. It then goes on to describe the chemical syntheses of nanoparticles with defined characteristics, their structural, electrical, and magnetic properties, as well as current methods to monitor these properties.

**Z55,137-6**

## SPECIAL TOPICS TITLES

### High-Throughput Screening in Chemical Catalysis: Technologies, Strategies and Applications

*A. Hagemeyer et al., Eds., Wiley, 2004, 339pp. Hardcover.* This is the first book to cover all of the important aspects of this field. The editors, from Symyx Technologies Inc., have assembled a group of distinguished authors, each contributing the most up-to-date results and status in their application of high-throughput methodologies. Each chapter is devoted to a major topic including: high-throughput micro-reactor and synthesis equipment technologies, analytical approaches, experimental design and testing strategies, and fully integrated workflows for materials discovery. Examples in chemical catalysis are presented with an emphasis on heterogeneous catalysis, olefin polymerization using homogeneous catalysts, and electrocatalysis for fuel cells.

**Z70,314-1**

### Patents, Copyrights and Trademarks for Dummies

*H. Charmasson, Wiley, 2004, 380pp. Softcover.* This book explains, in layman's terms, the basic nature, function, and application of intellectual property (IP) rights, including how you can acquire those rights, wield them effectively against your competitors, or exploit them lucratively through licensing agreements and other rewarding ventures. The book covers all of these critical concepts, such as working with IP professionals, presenting a patent explanation, determining what is copyrighted and what isn't, protecting your commercial identity, inspecting the basic elements of a license, determining infringement, and avoiding the ten worst naming blunders.

**Z70,281-1**

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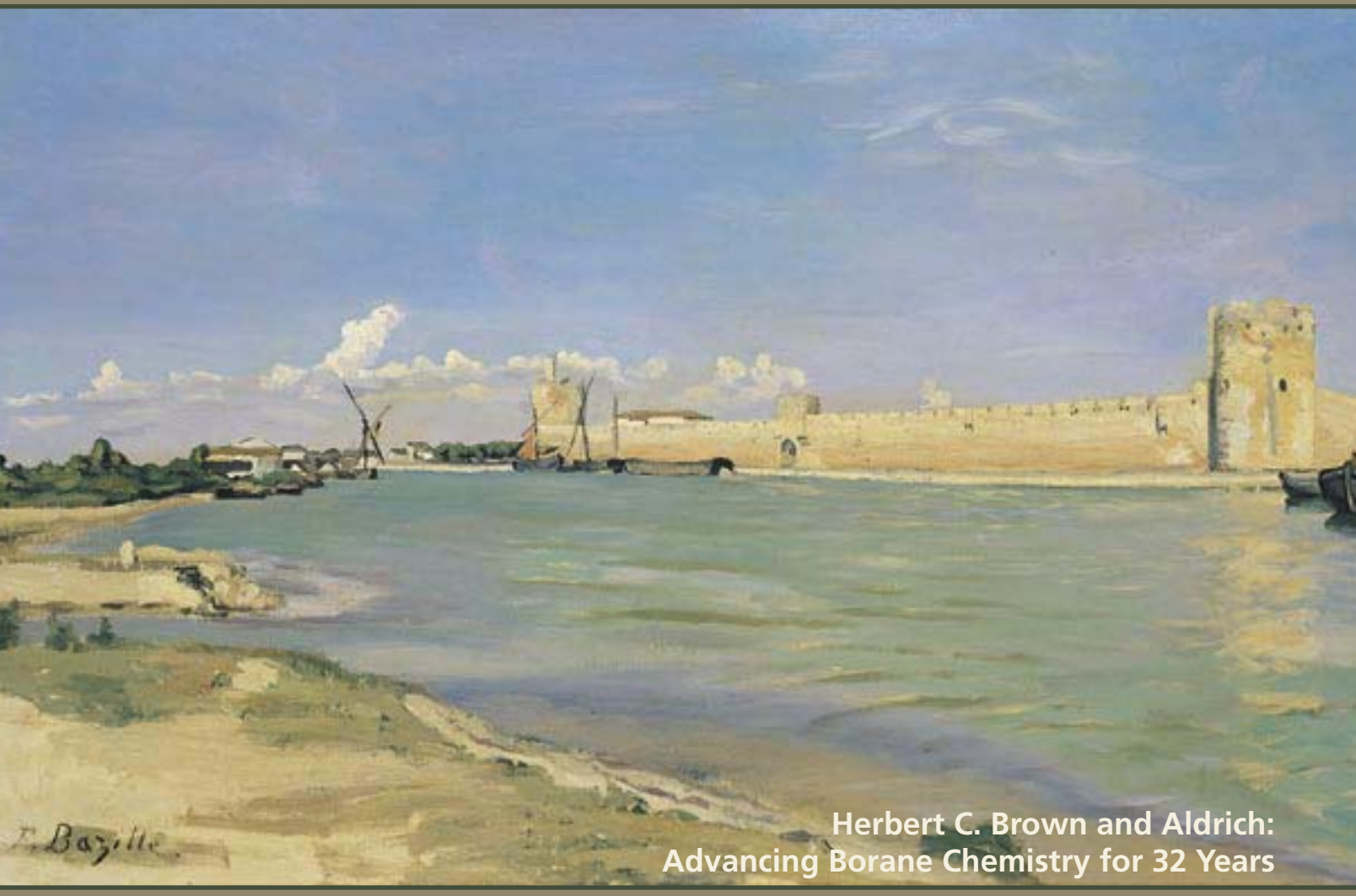
HONORING THE LIFE AND CONTRIBUTIONS OF H. C. BROWN

# Aldrichimica ACTA

VOL. 38, NO. 2 • 2005



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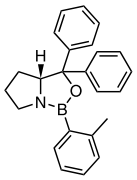
# New Products from Aldrich R&D

## REAGENTS FOR ASYMMETRIC SYNTHESIS

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

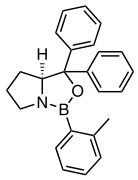
**65,429-9** 5 mL, 25 mL



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

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

**65,430-2** 5 mL, 25 mL

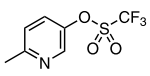


(1) Corey, E. J. et al. *J. Am. Chem. Soc.* **2002**, *124*, 3808. (2) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8106. (3) Ryu, D. H. et al. *J. Am. Chem. Soc.* **2002**, *124*, 9992. (4) Hu, Q.-Y. et al. *J. Am. Chem. Soc.* **2004**, *126*, 13708.

## REAGENTS FOR CROSS-COUPLING REACTIONS

### 2-Methylpyridin-5-yl trifluoromethanesulfonate, 97%

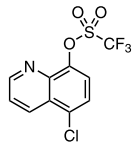
**64,848-5** 1 g, 5 g



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

### 5-Chloroquinolin-8-yl trifluoromethanesulfonate, 97%

**64,850-7** 1 g, 5 g



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

## LIGANDS FOR CATALYSIS

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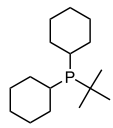
**65,532-5** 10 mL, 50 mL

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

### *tert*-Butyldicyclohexylphosphine, 97%

**65,160-5** 1 g, 5 g



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

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

## REAGENT FOR C–X BOND FORMATION

### Dimethyl thiophosphonate, 97%

**65,531-7** 1 g, 5 g

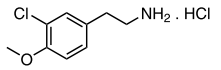
Reacts with imines under mild conditions and without demethylation to form α-aminophosphonothionates.

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

## BUILDING BLOCK

### 3-Chloro-4-methoxyphenethylamine hydrochloride

**65,632-1** 5 g



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

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

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

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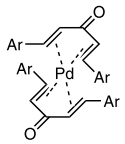
Joe Porwoll, President

Dr. Ian J. S. Fairlamb of the University of York, U.K., kindly suggested that we offer this Suzuki–Miyaura cross-coupling palladium catalyst in our catalog. Palladium-catalyzed cross-coupling reactions constitute some of the most important and applied transformations for the synthesis of natural products, pharmaceutical targets, and conjugated materials.[1] This palladium catalyst has shown a higher activity over $Pd_2(dba)_3$ in the Suzuki–Miyaura cross-coupling of organic halides with arylboronic acids.[2]


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


Ar = 3,5-dimethoxyphenyl

| | | |
|---|---|---|
| **65,693-3** | **Bis(3,5,3′,5′-dimethoxydibenzylideneacetone)-palladium(0)** [$Pd(dm\text{-}dba)_2$] | 1 g<br>5 g |

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

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

## TABLE OF CONTENTS



## ABOUT OUR COVER

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

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

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

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

# Organoboranes for Asymmetric Synthesis

## *From Sigma-Aldrich*

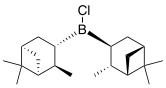
## DIP-Chloride™ and DIP-Bromide™

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

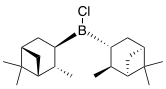
DIP-Bromide™ has been used for the asymmetric reduction of ketones, in enolboration reactions, and for the ring opening of meso epoxides.[6] Sigma-Aldrich is pleased to offer these excellent reagents for asymmetric synthesis to our customers.


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


**(+)-DIP-Chloride™**

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

**(–)-DIP-Chloride™**

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

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

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

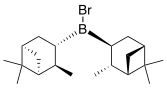
**(–)-DIP-Chloride™ solution, 50–65 wt. % in heptane**

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

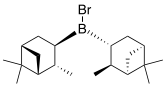
**(–)-DIP-Chloride™ solution, 50–65 wt. % in hexanes**

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

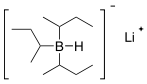
**(+)-DIP-Bromide™, 95%**

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

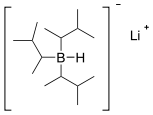
**(–)-DIP-Bromide™, 95%**

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

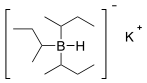
**L-Selectride® solution, 1.0 M in tetrahydrofuran**

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

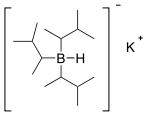
**LS-Selectride® solution, 1.0 M in tetrahydrofuran**

**22,592-4**  100 mL

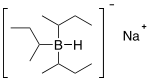
**K-Selectride® solution, 1.0 M in tetrahydrofuran**

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

**KS-Selectride® solution, 1.0 M in tetrahydrofuran**

**22,077-9**  100 mL

**N-Selectride® solution, 1.0 M in tetrahydrofuran**

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

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The Selectride® family of boranes is a group of powerful reagents for the asymmetric reduction of ketones on complex scaffolds. These reagents have been used in the synthesis of many natural products,[7] in the stereoselective reduction of hemiacetals in various nucleoside syntheses,[8] and are capable of effecting reductive cyclization[9] and rearrangement reactions.[10]


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


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

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

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## Outline



## 1. Introduction

Nobel Laureate Herbert C. Brown (HCB), the R. B. Wetherill Research Professor Emeritus of Chemistry at Purdue University, died on December 19, 2004, at age 92. He will long be remembered at Aldrich and by the scientific community for his extensive contributions to borane chemistry. Brown and Aldrich maintained a close working relationship that started in 1972 and continued until his death. Interested readers are directed to his published obituary[1] and to the HCB pages on the Purdue University Department of Chemistry Web site.[2] A number of essays and notes have also appeared in this magazine, which provide biographical information and additional details about HCB and his 32-year relationship with Aldrich.[3]

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

## 2. Before 1972

The late 1960s were exciting times in HCB's research group at Purdue. We were actively investigating hydroboration and the reactions of organoboranes. The work was being quickly published as a series of communications in various journals.[4] However, Brown knew his developments would not be widely used until his new borane reagents were made available commercially.

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

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

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

## 3. Aldrich-Boranes, Inc.

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

## 4. Early Borane Reagents

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

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

HCB was not only a great scientist, but also a good businessman. He took an interest in all aspects of our business, especially the advertising and promotion of our products. He encouraged me to expand some of our advertisements into detailed reviews suitable for publications. These were published in various refereed journals and then condensed into shorter reviews for this magazine.[6] In addition, HCB contributed a review on the subject and encouraged one of his postdoctoral assistants to submit another.[7] These helped promote our borane products and contributed greatly to our early success.

## 5. Boranes on a Large Scale

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

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

## 6. Latest Borane Reagents

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

## 7. Philanthropy

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

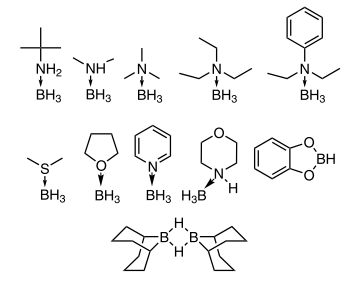


**Figure 1.** Early Borane Reagents Developed and Offered by Aldrich.

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

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

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

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

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

## 8. Conclusions

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

In 1972, Aldrich's motto was "Craftsmen in Chemistry", which was very appropriate for both HCB and the Aldrich chemists at that time. Later, Aldrich changed its motto to "Chemists Helping Chemists in Research and Industry", which was how HCB also approached his contributions to synthetic chemistry. He always wanted his reagents to be used by others in their research. Today, Aldrich's motto is "Advancing Science". There is no question that Herbert C. Brown worked his entire life to advance borane science. He will be missed, but we will continue to explore and develop the borane chemistry he first discovered.

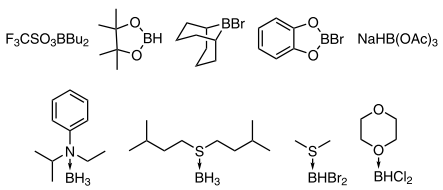


**Figure 3.** Representative List of the Latest Borane Reagents.

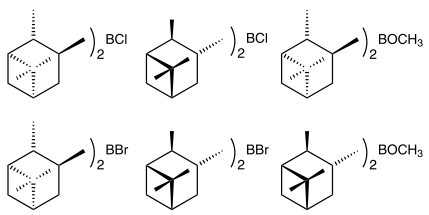


**Figure 4.** α-Pinene-Derived Borane Reagents.

## 9. References and Notes

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(2) http://www.chem.purdue.edu/hcbrown/ (accessed February 2005). Please note especially the links to Biography, HCB Story (autobiographical); Purdue Lecture; 1979 Nobel Prize with a PDF file of the HCB Nobel lecture of December 8, 1979; and a bibliographical archive listing all of HCB's patents (total of 63), publications (total > 1200), the 22 M.S. degree theses, and the 141 Ph.D. theses of HCB's former students.

(3) (a) Brewster, J. H. *Aldrichimica Acta* **1987**, *20*, 3. (b) Davenport, D. A. *Aldrichimica Acta* **1987**, *20*, 25. (c) Firsan, S. J. *Aldrichimica Acta* **2001**, *34*, 35. (d) Herbert C. Brown and Aldrich (*Editor's note*). *Aldrichimica Acta* **2002**, *35*, 2.

(4) For a review covering this early period of organoborane research, see Brown, H. C. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975. (Reprinted as *Organic Syntheses via Boranes, Volume 1* by Aldrich Chemical Company, Inc.; Cat. No. Z40,094-7.)

(5) (a) Schlesinger, H. I.; Brown, H. C. *J. Am. Chem. Soc.* **1940**, *62*, 3429. (b) Schlesinger, H. I.; Brown, H. C.; Finholt, A. E. *J. Am. Chem. Soc*. **1953**, *75*, 205.

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## About the Author

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

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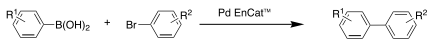


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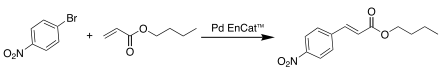


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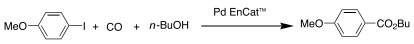


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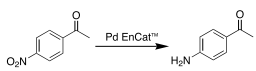


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**References:** (1) Yu, J.-Q. et al. *Chem Commun.* **2003**, 678. (2) Bremeyer, N. et al. *Synlett* **2002**, 1843. (3) Ley, S. V. et al. *Chem Commun.* **2002**, 1134. (4) Chandrashekar, R. et al. *Chem Commun.* **2002**, 1132. (5) Vickerstaffe,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

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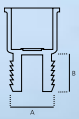

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| 25 | 14.0 | 14.1 | 12.5 | ₸14/20 joints | **Z16,728-2** | **Z12,459-1** |
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| 37 | 19.0 | 20.4 | 15.7 | ₸19/22 joints | **Z16,730-4** | **Z12,462-1** |
| 45 | 22.0 | 23.0 | 20.4 | ₸24/40 joints | **Z16,732-0** | **Z12,465-6** |
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# Organotrifluoroborates: Expanding Organoboron Chemistry


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## Outline



## 1. Introduction

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

Even though the chemistry of organotrifluoroborates has been comprehensively reviewed elsewhere,[2] the recent growth in the application of these compounds warrants another look. The present review outlines the utility and versatility of organotrifluoroborates in cross-coupling reactions. Additionally, the ability of these reagents to resist chemical oxidation will be highlighted. This feature of organotrifluoroborates offers a unique opportunity to preserve the carbon–boron bond in the oxidation of remote functionality within the same molecule.

## 2. Preparation of Potassium Organotrifluoroborates

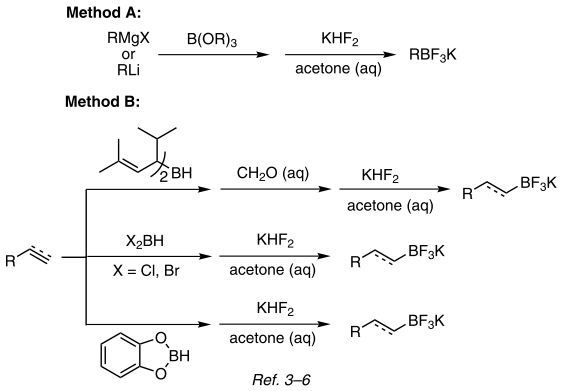
Although potassium organotrifluoroborates have been known for some time, Vedejs and co-workers were the first to report the most convenient synthesis of these materials from boronic acids and derivatives utilizing the readily available and inexpensive $KHF_2$.[3] In combination with this facile process,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

## 3. Suzuki Cross-Coupling Reactions

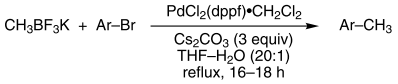
Early studies by the groups of Genêt[7] and Xia[8] demonstrated the potential of organotrifluoroborates in palladium-catalyzed coupling reactions to form biaryls using arenediazonium salts or diaryliodonium salts as electrophiles. It should be noted that organotrifluoroborates led to superior yields and reactivity in side-by-side comparisons with boronic acids.[9] Since those early studies, the scope of cross-coupling reactions that utilize organotrifluoroborates has expanded considerably.

### *3.1. Alkyltrifluoroborates*

The first cross-coupling reactions of alkyltrifluoroborates with aryl halides were efficiently performed using $PdCl_2$(ddpf) as the catalyst, $Cs_2CO_3$ as the base, and THF–$H_2O$ as the solvent system, and showed tolerance of a number of functional groups (**eq 1**).[10,11]




**Scheme 1**. The Two General Methods for Preparing Organotrifluoroborates.

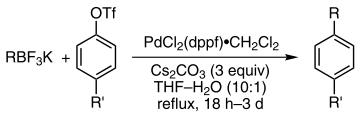



dppf = 1,1'-bis(diphenylphosphino)ferrocene

| Ar | Yield | Ar | Yield |
|---|---|---|---|
| 4-PhC(O)$C_6H_4$ | 92% | 2-N$CC_6H_4$ | 60% |
| 4-AcNH$C_6H_4$ | 67% | 3-$MeO_2CC_6H_4$ | 57% |
| 4-$O_2NC_6H_4$ | 77% | 2-$F_3C$-4-$O_2NC_6H_3$ | 83% |
| 4-N$CC_6H_4$ | 68% | 2-Ac$C_6H_4$ | 61% |

*Ref. 11*

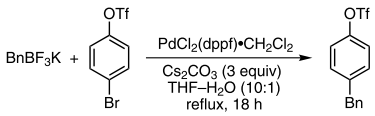
**eq 1**




| R | R' | Yield |
|---|---|---|
| Bn | 4-$NO_2$ | 89% |
| N$C(CH_2)_5$ | 4-$NO_2$ | 73% |
| $H_3CC(O)(CH_2)_4$ | 4-Ac | 79% |
| Cl$(CH_2)_3$ | 4-Ac | 72% |
| Bz$O(CH_2)_3$ | 4-Ac | 70% |
| TsN$H(CH_2)_3$ | 4-Ac | 75% |
| Ph$S(CH_2)_3$ | 4-Ac | 66% |

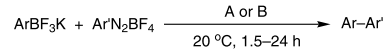
*Ref. 10,11*

**eq 2**




*Ref. 10,11*

**eq 3**




| Ar | Ar' | Cond.[a] | Yield[b] |
|---|---|---|---|
| Ph | 4-$MeC_6H_4$ | A | (88%) |
| 4-$FC_6H_4$ | 4-$O_2NC_6H_4$ | A | 92% |
| thien-3-yl | 3-Bz$C_6H_4$ | A | 86% |
| 2,4-$Cl_2C_6H_3$ | 4-$EtO_2CC_6H_4$ | A | (26%) |
| 2,4-$Cl_2C_6H_3$ | 4-$EtO_2CC_6H_4$ | B | 73% |
| 1-naphthyl | 4-Br-2,6-$Me_2C_6H_2$ | A | 21% |
| 1-naphthyl | 4-Br-2,6-$Me_2C_6H_2$ | B | (10%) |
| Ph | 2,4-$(MeO)_2C_6H_3$ | A | 69% |

[a] Conditions A: $Pd(OAc)_2$, 1,4-dioxane; conditions B: $Pd_2(\mu\text{-}OAc)_2[P(o\text{-tolyl})_3]_2$, MeOH.
[b] Isolated yields. GC yields are in parentheses.

*Ref. 7a*

**eq 4**

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

Aryl triflates, common coupling partners in palladium-catalyzed cross-coupling reactions, were as efficient as the aryl halides (**eq 2**).[10,11] Surprisingly, the nitro group survived the basic reaction conditions, when *p*-nitrophenyl triflate was reacted with potassium benzyltrifluoroborate. By contrast, the nitro group is reduced to the corresponding aniline product in Suzuki reactions with *B*-alkyl-9-BBN.[14] The electrophiles employed showed the same relative reactivity order as that observed with organotin[15] and *B*-alkyl-9-BBN[14] reagents, i.e., Br > OTf >> Cl (**eq 3**).[10] The use of secondary alkyltrifluoroborates was prohibited by the predominance of β-elimination and dehydroboronation pathways.

### 3.2. Aryltrifluoroborates

The use of aryltrifluoroborates in Suzuki-type reactions was first reported by Genêt's and Xia's groups. Genêt and co-workers[7] reported the reaction of arenediazonium tetrafluoroborates with aryltrifluoroborates using two catalyst systems: $Pd(OAc)_2$ in 1,4-dioxane (A) and $Pd_2(\mu\text{-}OAc)_2[P(o\text{-tolyl})_3]_2$ in MeOH (B) (**eq 4**).[7a] These systems were tolerant of different functional groups and, in the case of the *ortho*-chloro-substituted aryltrifluoroborate, only conditions B were efficient due to the precipitation of metallic palladium when using conditions A. The reaction was also chemoselective toward the arenediazonium salt in the presence of halides or triflates.

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

Subsequently, the reaction of aryltrifluoroborates with aryl halides as coupling partners was developed (**eq 7**).[12,16] Specifically, a key point was the discovery that the use of a base was required. As previously observed by Xia, many of the reactions could be performed under ligandless conditions. A variety of trifluoroborates were reacted using $Pd(OAc)_2$ as the catalyst and inexpensive $K_2CO_3$ as the base. The choice of solvent for these cross-couplings was critical because of solubility issues associated with trifluoroborates. Another added feature of these reactions was their insensitivity to oxygen: excellent results were obtained whether the reactions were carried out in an inert atmosphere or in the air. The coupling of potassium phenyltrifluoroborate with a variety of electron-rich aryl halides afforded the corresponding biaryls in good-to-excellent yields. The slight decrease in yield using amide or amine substituents might be due to their complexation with the palladium catalyst.[17]

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

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

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

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

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

### 3.3. Heteroaryltrifluoroborates

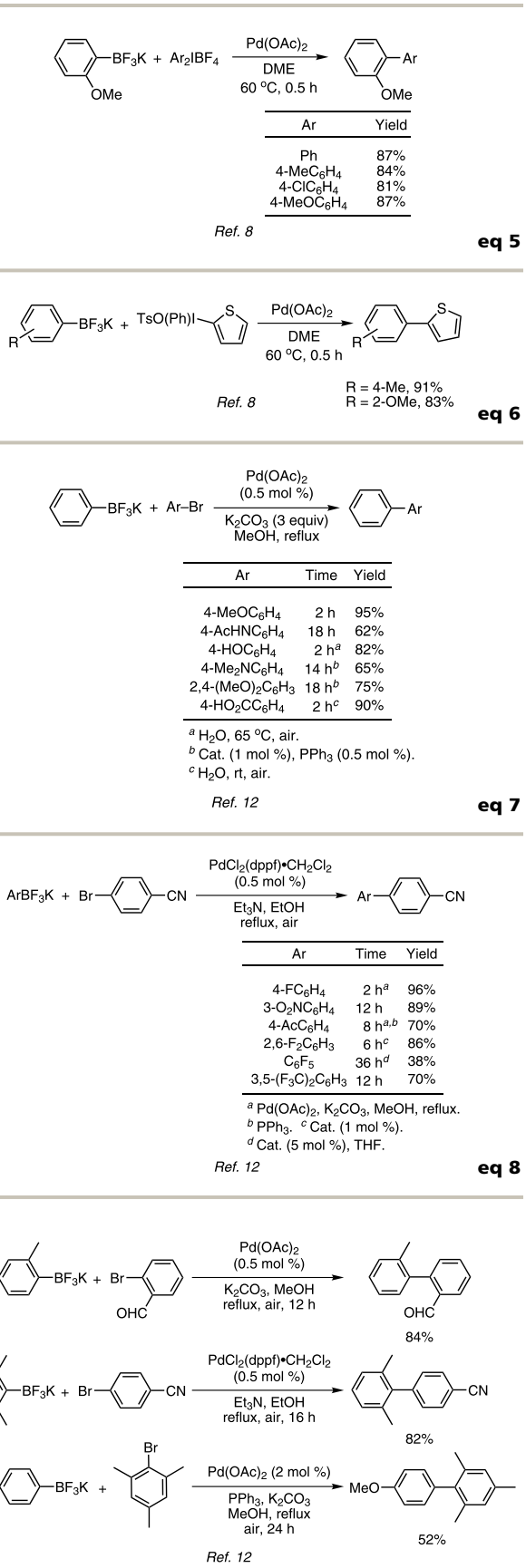
The Suzuki-type reactions were expanded to the use of heteroaryltrifluoroborates and a number of diverse heteroaryl bromides as coupling partners (**eq 11**).[12] Activated heteroaryl halides such as 3-bromopyridine require a shorter reaction time than 2-bromopyridine. These heteroaryl halides also reacted under ligandless conditions. Unactivated thiophenes and thiazoles required longer reaction times and the use of $PdCl_2(dppf)•CH_2Cl_2$. In some cases, this led to homocoupling of the trifluoroborate. It is of interest that reaction of the unprotected 7-bromoindole gave 77% of the expected biaryl. It is believed in this case that the basic, ligand-added conditions inhibited complexation of the indole nitrogen to the palladium.[12]

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

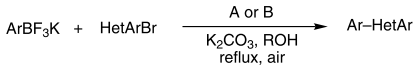
### 3.4. Alkenyltrifluoroborates

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

Initial studies with functionalized aryl electrophiles demonstrated that the coupling reaction using $PdCl_2(dppf)•CH_2Cl_2$ could be accomplished using both halides and triflates (**eq 12**).[21,22] The reactions were run in *i*-PrOH–$H_2O$ using *t*-$BuNH_2$ as the inexpensive base. It is important to mention that the conditions developed for the coupling of alkyltrifluoroborates [$PdCl_2(dppf)•CH_2Cl_2$, $Cs_2CO_3$, THF–$H_2O$] were also efficient. A variety of functional groups (e.g., nitro, cyano, aldehyde, ketone, ether) were tolerated in these reactions. The reactions were efficient with variously substituted alkenyltrifluoroborates, from the parent vinyltrifluoroborate to trisubstituted analogs (**eq 13**).[22] The double-bond geometry of the trifluoroborate was retained with complete stereospecificity in these reactions. Batey and Quach have reported that tetrabutylammonium




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

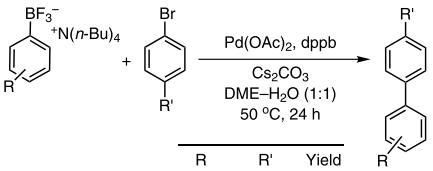



| Ar | HetAr | Cond.[a] | Time | Yield |
|---|---|---|---|---|
| Ph | pyridin-2-yl | A | 5 h | 70% |
| Ph | pyridin-3-yl | A[b] | 2 h | 90% |
| Ph | pyrimidin-5-yl | A[b] | 5 h | 92% |
| Ph | 2-acetylthien-5-yl | A | 0.8 h | 93% |
| Ph | 2-carboxyfuran-5-yl | A[c] | 6 h | 67% |
| 1-naphthyl | thien-2-yl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

[a] Conditions A: $Pd(OAc)_2$ (0.5–1.0 mol %), MeOH; conditions B: $PdCl_2(dppf)•CH_2Cl_2$ (1–2 mol %), $Et_3N$, EtOH. [b] $Pd(OAc)_2$ (1.0 mol %). [c] $H_2O$, 65 °C. [d] HetArCl.

*Ref. 12*

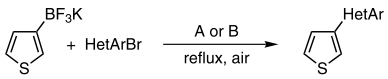
**eq 9**




| R | R' | Yield |
|---|---|---|
| 4-Ac | 4-OHC | 75% |
| 3-Cl | 4-Ac | 92% |

*Ref. 13*

**eq 10**

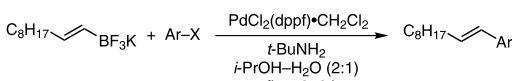



| HetAr | Cond.[a] | Time | Yield |
|---|---|---|---|
| pyridin-2-yl | A | 15 h | 60% |
| pyridin-3-yl | A | 7 h | 68% |
| thiazol-2-yl | B | 14 h | 67% |
| thien-2-yl | B | 13 h | 63% |
| 2-carboxyfuran-5-yl | B | 10 h[b] | 70% |
| pyrazin-2-yl | B | 12 h[b,c] | 83% |
| pyrimidin-5-yl | B | 18 h | 75%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

[a] Conditions A: $Pd(OAc)_2$ (0.5–1 mol %), $K_2CO_3$, MeOH; conditions B: $PdCl_2(dppf)•CH_2Cl_2$ (0.5–2 mol %), $NEt_3$, EtOH. [b] $K_2CO_3$ used instead of $Et_3N$. [c] HetArCl.

*Ref. 12*

**eq 11**




| Ar | X | Yield |
|---|---|---|
| 4-$MeOC_6H_4$ | I | 60% |
| 4-$O_2NC_6H_4$ | Br | 71% |
| 4-$O_2NC_6H_4$ | OTf | 76% |
| 4-$AcC_6H_4$ | Br | 69% |

*Ref. 22*

**eq 12**

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

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

Cross-coupling of alkenyltrifluoroborates with alkenyl halides results in the preparation of conjugated dienes which are important synthetic units. Conjugated dienes are present in many biologically active compounds, and serve as starting materials in the highly useful Diels–Alder reaction. Although many other methods of synthesis of conjugated dienes are available, these have many limitations. The Kumada[23] and Negishi[24] coupling reactions sometimes provide low chemoselectivities and yields, and often create operational difficulties as well. For example, both are air-sensitive and the starting materials are usually prepared in situ. The tin reagents utilized in the Stille coupling are toxic, and the tin-containing byproducts formed in the coupling are difficult to remove. Some of the limitations of alkenylboronic acid derivatives have been mentioned above. Additionally, the added requirement of having to use excess amounts of toxic thallium bases to achieve efficiency in cross-coupling reactions of alkenylboronic acids and alkenylboronate esters with alkenyl halides further limits the usefulness of these organoboron reagents.[25]

The Suzuki-type reactions of alkenyltrifluoroborates with alkenyl halides were performed using optimized conditions [$Pd(OAc)_2$, 2 $PPh_3$, $Cs_2CO_3$, THF–$H_2O$] (**eq 16**).[26] The system was sensitive to air and thus inert atmosphere conditions were required. Initial studies revealed that the process is completely stereospecific. Thus, the reaction of (*E*)- and (*Z*)-4-phenyl-1-buten-1-yltrifluoroborate with (*E*)- and (*Z*)-1-bromo-5-chloro-1-pentene resulted in the synthesis of the four possible isomers in a stereodefined manner (>99%). Interestingly, the reaction was not susceptible to steric hindrance within the halide partner. Highly substituted alkenyl bromides afforded the dienes in high yields. Additionally, many functional groups (e.g., formyl and cyano) were tolerated.[26] In particular, the reaction with 2-bromo-3-methyl-2-cyclopenten-1-one was of interest, because α-bromoenones were previously found to be unreactive under other coupling conditions.[27]

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

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

### 3.5. Alkynyltrifluoroborates

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

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

Subsequently, a successful protocol for the Suzuki cross-coupling of potassium alkynyltrifluoroborates with the more accessible aryl halides and triflates was developed. Thus, the cross-coupling reaction of potassium 1-hexyn-1-yltrifluoroborate, using $PdCl_2(dppf)•CH_2Cl_2$ as the catalyst, with various aryl bromides proceeded in good yields (**eq 19**).[33] Surprisingly, alcohols and carboxylic acids were tolerated in the reaction, even though, in principle, protodeboronation of the alkynyltrifluoroborate with these functional groups is a distinct possibility.[2,12,34] Heteroaryl bromides were also effective coupling partners.

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

### 3.6. Synthetic Application

The first application of organotrifluoroborates in natural product synthesis was demonstrated in the formal total synthesis of oximidine II.[35] Oximidines are natural products with a diverse biological activity.[36] The challenge in these targets was the construction of the highly strained macrolide. The key step in this synthesis was the macrocyclization of an alkenyltrifluoroborate to accomplish the formation of the 12-membered ring (**Scheme 3**).[35] The reaction was performed under previously developed Suzuki-type reaction conditions as discussed above. This approach afforded several advantages over traditional macrolactonization reactions that had been attempted previously, and its success was due to the ease of access of the trifluoroborate functionality via the Snieckus hydroboration[37] and the inherent stability of the resulting boron derivative.

## 4. Oxidation Reactions

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

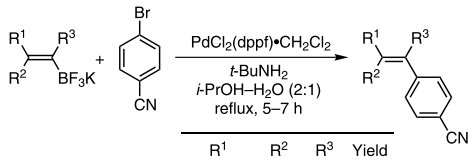
### 4.1. Epoxidation

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

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

### 4.2. Ozonolysis

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

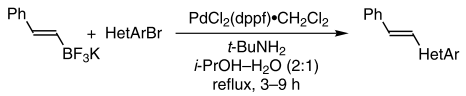



| $R^1$ | $R^2$ | $R^3$ | Yield |
|---|---|---|---|
| H | H | H | 76%[a] |
| H | H | Me | 70% |
| H | Ph | H | 86% |
| $n$-$C_8H_{17}$ | H | H | 87% |
| $Cl(CH_2)_3$ | H | H | 52% |
| Et | H | Et | 70% |

[a] $Et_3N$ used as base.

*Ref. 22*

**eq 13**

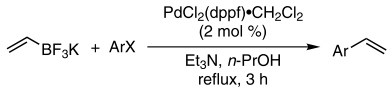



| HetAr | Yield |
|---|---|
| thien-3-yl | 80% |
| 2-acylthien-5-yl | 91% |
| thiazol-2-yl[a] | 83% |
| pyridin-2-yl | 70% |
| pyrimidin-5-yl | 73% |
| indol-7-yl | 70% |

[a] $Et_3N$ used as base.

*Ref. 22*

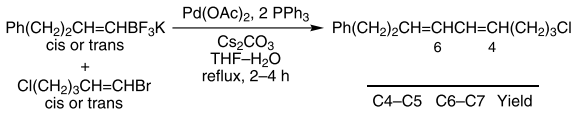
**eq 14**




| Ar | X | Yield |
|---|---|---|
| 4-methoxyphenyl | OTf | 64% |
| 2-formylphenyl | Br | 65% |
| 3-nitropyridin-2-yl | Cl | 62% |
| 1-naphthyl | Br | 75% |
| 2-acylthien-5-yl | Br | 60% |

*Ref. 21*

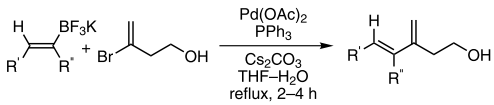
**eq 15**




| C4–C5 | C6–C7 | Yield |
|---|---|---|
| cis | cis | 86% |
| cis | trans | 88% |
| trans | cis | 85% |
| trans | trans | 86% |

*Ref. 26*

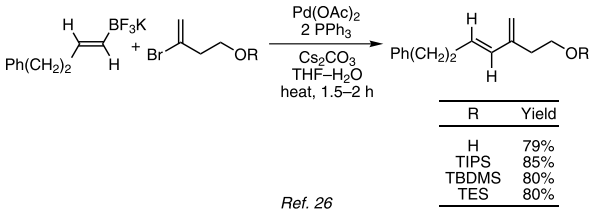
**eq 16**




| R' | R" | Yield |
|---|---|---|
| Et | Et | 66% |
| $Cl(CH_2)_4$ | H | 72% |
| $NC(CH_2)_2$ | H | 80% |
| $MeO_2C(CH_2)_3$ | H | 70% |

*Ref. 26*

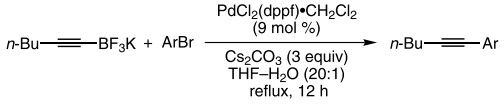
**eq 17**




| R | Yield |
|---|---|
| H | 79% |
| TIPS | 85% |
| TBDMS | 80% |
| TES | 80% |

*Ref. 26*

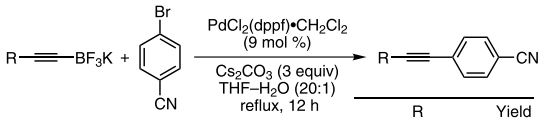
**eq 18**




| Ar | Yield |
|---|---|
| 4-$Me_2NC_6H_4$ | 61% |
| 4-$HOCH_2C_6H_4$ | 76% |
| 1,3-benzodioxol-5-yl[a] | 75% |
| 4-$HO_2CC_6H_4$ | 73% |
| 2-$OHCC_6H_4$[a] | 89% |
| 4-$NCC_6H_4$ | 98% |
| indol-7-yl[a] | 97% |
| 2-acetylthien-5-yl[a] | 88% |
| thiazol-2-yl | 78% |

*Ref. 33* [a] In anhydrous THF.

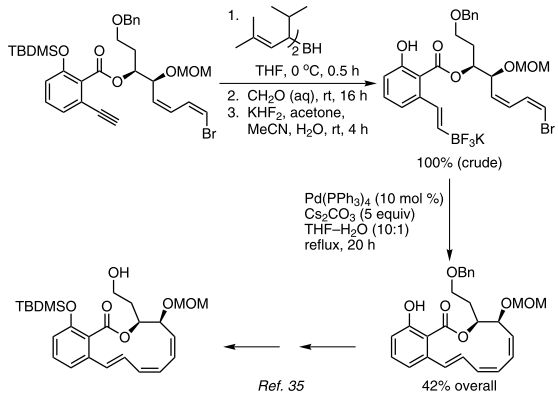
**eq 19**



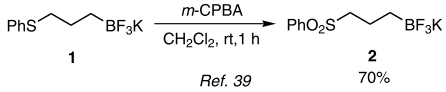

| R | Yield |
|---|---|
| $n$-$C_8H_{17}$ | 91% |
| 3-$Cl(CH_2)_3$ | 85% |
| $Ph(CH_2)_2$ | 92% |
| $H_2C{=}C(Me)$ | 87% |
| $TBDMSO(CH_2)_2$ | 88% |
| TMS | 60% |

*Ref. 33*

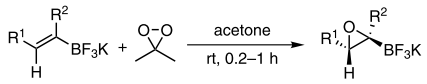
**eq 20**




**Scheme 3**. Formal Total Synthesis of Oximidine II.



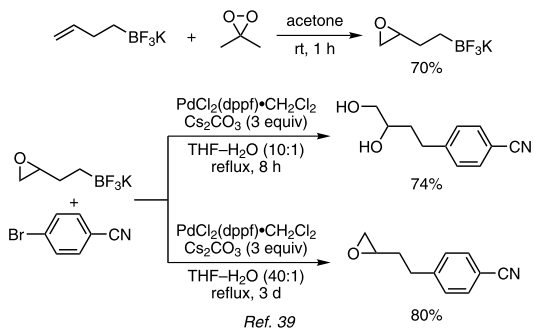

**eq 21**



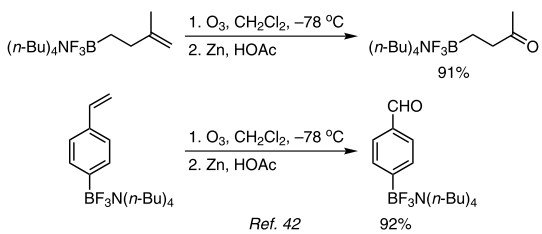

| $R^1$ | $R^2$ | Yield |
|---|---|---|
| $n$-$C_8H_{17}$ | H | 85% |
| Ph[a] | H | 70% |
| $ClCH_2$ | H | 71% |
| H | Me | 80% |

*Ref. 39* [a] At –78 °C.

**eq 22**




**Scheme 4**. Reaction Conditions for the Retention and Opening of the Oxirane Ring in the Suzuki-Type Cross-Coupling Reaction.




**Scheme 5**. The Compatibility of Trifluoroborates with Ozonolysis Conditions.

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

## 5. Conclusions

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

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## About the Authors

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

Professor Molander's research interests center on the development of new methods for organic synthesis and natural product synthesis. A major focus of his research has been the application of organolanthanide reagents and catalysts to selective organic synthesis. To date, more than 170 research papers have emanated from his research program. He has received several honors for his work, including an Alfred P. Sloan Foundation Fellowship (1987), the American Cyanamid Academic Award (1989), the Arthur C. Cope Scholar Award from the American Chemical Society (ACS) in 1998, a Japanese Society for the Promotion of Science Fellowship (2002), and the Philadelphia Section Award of the ACS (2003). He has been a Visiting Professor at the Université de Paris-Sud, Orsay, France (1989, 1997); Philipps Universität, Marburg, Germany (1989); École Supérieure de Physique et de Chimie Industrielles de Paris (1993); Universidade Federal da Paraíba, Brazil (1998); Universidade Federal de Pernambuco, Brazil (1998); Universidad Nacional del Litoral, Santa Fe, Argentina (1998); Institute of Organometallic Chemistry, Russian Academy of Sciences, Nizhny Novgorod, Russia (1998); the Institut de Recherche en Chimie Organique Fine, Rouen, France (1999), and the Universidade Federal de Santa Maria, Brazil (2001).

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

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


# New Trifluoroborate Salts for Suzuki Coupling
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**Potassium vinyltrifluoroborate, 95%**
65,522-8 — 1 g, 5 g

**Potassium 2-methoxyphenyltrifluoroborate**
65,493-0 — 1 g, 5 g

**Potassium 5-methyl-2-thiophenetrifluoroborate**
65,494-9 — 1 g, 5 g

**Potassium 2-naphthalenetrifluoroborate**
65,701-8 — 1 g, 5 g

**Potassium 4-*tert*-butylphenyltrifluoroborate, 95%**
65,472-8 — 1 g, 10 g

**Potassium 2,4-difluorophenyltrifluoroborate**
65,699-2 — 1 g, 5 g

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

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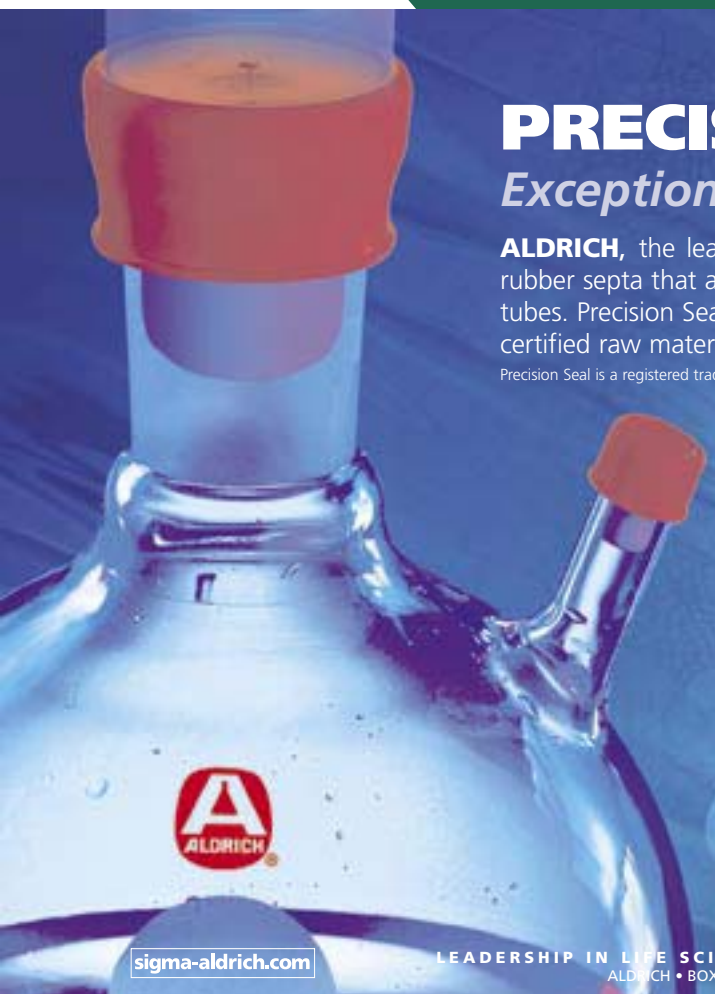


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| 8-mm o.d. glass tubing | Z55,391-3 | Z55,403-0 |
| 10-mm o.d. glass tubing | Z55,392-1 | Z55,404-9 |
| 13-mm i.d. tubing | Z55,394-8 | Z55,405-7 |
| 10/30 joints | Z55,395-6 | Z55,406-5 |
| 14/20 joints | Z55,396-4 | Z55,407-3 |
| 19/22 joints | Z55,397-2 | Z55,408-1 |
| 24/40 joints | Z55,398-0 | Z55,410-3 |
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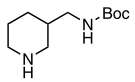
## *Organic Reagents and Building Blocks*

### 3-(Boc-aminomethyl)piperidine, 95%

**65,389-6**
$C_{11}H_{22}N_2O_2$



1 g
10 g

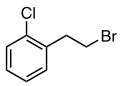
### 2,3,5,6-Tetramethylbenzaldehyde

**56,500-8**
$C_{11}H_{14}O$

5 g

### 2-Chlorophenethyl bromide, 97%

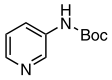
**65,501-5**
$C_8H_8BrCl$



1 g
5 g

### 3-(Boc-amino)pyridine, 97%

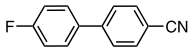
**65,550-3**
$C_{10}H_{14}N_2O_2$



1 g
10 g

### 4-(4-Fluorophenyl)benzonitrile, 97%

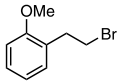
**64,992-9**
$C_{13}H_8FN$



1 g
5 g

### 2-Methoxyphenethyl bromide, 97%

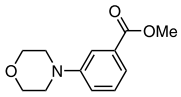
**65,503-1**
$C_9H_{11}BrO$



1 g
5 g

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

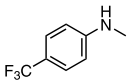
**65,470-1**
$C_{12}H_{15}NO_3$



1 g
5 g

### *N*-Methyl-4-trifluoromethylaniline, 97%

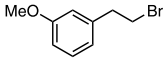
**63,105-1**
$C_8H_8F_3N$



1 g
5 g

### 3-Methoxyphenethyl bromide, 97%

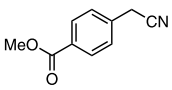
**65,533-3**
$C_9H_{11}BrO$



1 g
5 g

### Methyl 4-(cyanomethyl)benzoate, 96%

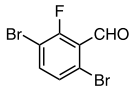
**65,559-7**
$C_{10}H_9NO_2$



5 g
25 g

### 3,6-Dibromo-2-fluorobenzaldehyde

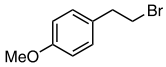
**65,239-3**
$C_7H_3Br_2FO$



1 g
5 g

### 4-Methoxyphenethyl bromide, 97%

**65,515-5**
$C_9H_{11}BrO$



1 g
5 g

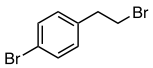
### 2,3,5,6-Tetramethylbenzoic acid

**56,501-6**
$C_{11}H_{14}O_2$

5 g

### 4-Bromophenethyl bromide, 96%

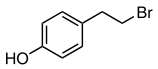
**65,198-2**
$C_8H_8Br_2$



1 g
10 g

### 4-Hydroxyphenethyl bromide, 96%

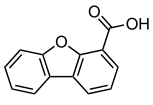
**65,202-4**
$C_8H_9BrO$



1 g
10 g

### Dibenzofuran-4-carboxylic acid, 97%

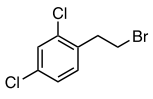
**56,283-1**
$C_{13}H_8O_3$



1 g

### 2,4-Dichlorophenethyl bromide, 96%

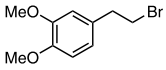
**65,382-9**
$C_8H_7BrCl_2$



1 g
5 g

### 3,4-Dimethoxyphenethyl bromide, 97%

**65,367-5**
$C_{10}H_{13}BrO_2$

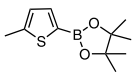


1 g
5 g

# Boronic Acids and Esters

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

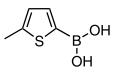
**65,507-4**
$C_{11}H_{17}BO_2S$



1 g
10 g

### 5-Methyl-2-thiopheneboronic acid

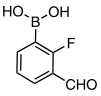
**51,219-2**
$C_5H_7BO_2S$



1 g
5 g

### 2-Fluoro-3-formylphenylboronic acid

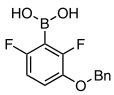
**64,578-8**
$C_7H_6BFO_3$



1 g
5 g

### 3-Benzyloxy-2,6-difluorophenylboronic acid

**63,570-7**
$C_{13}H_{11}BF_2O_3$



1 g
5 g

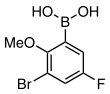
### 6-Bromo-2,3-difluorophenylboronic acid

**63,577-4**
$C_6H_4BBrF_2O_2$

1 g
5 g

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

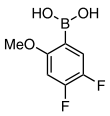
**64,517-6**
$C_7H_7BBrFO_3$



1 g
5 g

### 4,5-Difluoro-2-methoxyphenylboronic acid

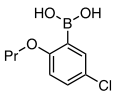
**64,518-4**
$C_7H_7BF_2O_3$



1 g
5 g

### 5-Chloro-2-propoxyphenylboronic acid

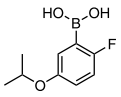
**64,519-2**
$C_9H_{12}BClO_3$



1 g
5 g

### 2-Fluoro-5-isopropoxyphenylboronic acid

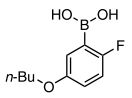
**64,520-6**
$C_9H_{12}BFO_3$



1 g
5 g

### 5-Butoxy-2-fluorophenylboronic acid

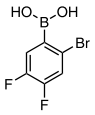
**64,523-0**
$C_{10}H_{14}BFO_3$



1 g
5 g

### 2-Bromo-4,5-difluorophenylboronic acid

**64,528-1**
$C_6H_4BBrF_2O_2$



1 g
5 g

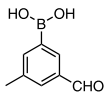
### 3-Bromo-5-methylphenylboronic acid

**64,531-1**
$C_7H_8BBrO_2$

1 g
5 g

### 3-Formyl-5-methylphenylboronic acid

**64,533-8**
$C_8H_9BO_3$



1 g

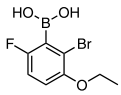
### 3-Bromo-5-fluorophenylboronic acid

**64,534-6**
$C_6H_5BBrFO_2$

1 g
10 g

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

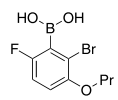
**64,571-0**
$C_8H_9BBrFO_3$



1 g
5 g

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

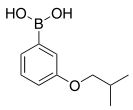
**64,572-9**
$C_9H_{11}BBrFO_3$



1 g
5 g

### 3-Isobutoxyphenylboronic acid

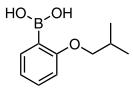
**64,573-7**
$C_{10}H_{15}BO_3$



1 g
5 g

### 2-Isobutoxyphenylboronic acid

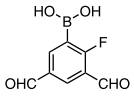
**64,574-5**
$C_{10}H_{15}BO_3$



1 g
5 g

### 3,5-Diformyl-2-fluorophenylboronic acid

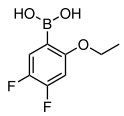
**64,579-6**
$C_8H_6BFO_4$



1 g
5 g

### 4,5-Difluoro-2-ethoxyphenylboronic acid

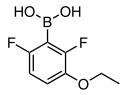
**65,094-3**
$C_8H_9BF_2O_3$



1 g
5 g

### 2,6-Difluoro-3-ethoxyphenylboronic acid

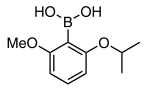
**65,095-1**
$C_8H_9BF_2O_3$



2 g
10 g

### 2-Isopropoxy-6-methoxyphenylboronic acid

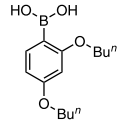
**65,097-8**
$C_{10}H_{15}BO_4$



2 g
10 g

### 2,4-Dibutoxyphenylboronic acid

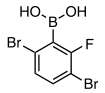
**65,099-4**
$C_{14}H_{23}BO_4$



1 g
5 g

### 3,6-Dibromo-2-fluorophenylboronic acid

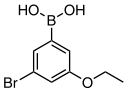
**65,108-7**
$C_6H_4BBr_2FO_2$



2 g
10 g

### 5-Bromo-3-ethoxyphenylboronic acid

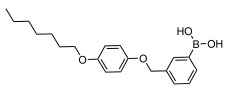
**65,119-2**
$C_8H_{10}BBrO_3$



1 g
5 g

### 3-(4′-Heptyloxyphenoxymethyl)phenylboronic acid

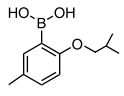
**65,121-4**
$C_{20}H_{27}BO_4$



1 g
5 g

### 2-Isobutoxy-5-methylphenylboronic acid

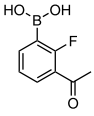
**65,123-0**
$C_{11}H_{17}BO_3$



2 g
10 g

### 3-Acetyl-2-fluorophenylboronic acid

**65,124-9**
$C_8H_8BFO_3$



2 g
10 g

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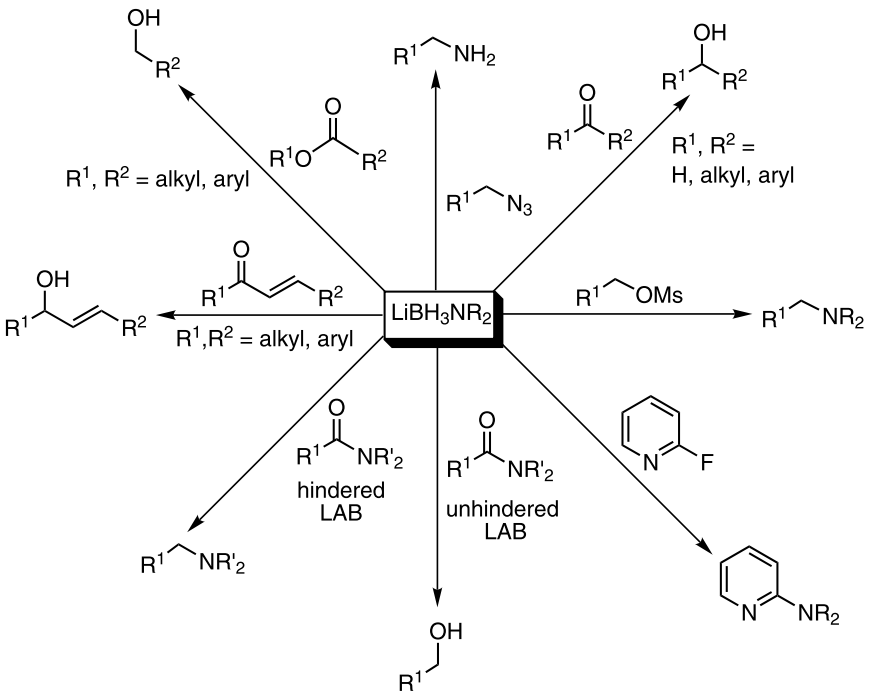
# Lithium Aminoborohydride (LAB) Reagents

## *Powerful, Air-Stable, and Selective Reducing Agents*




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

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

**Lithium dimethylaminoborohydride solution, 1 M in THF**

| | | |
|---|---|---|
| **65,823-5** | | 25 mL |
| $C_2H_9BLiN$ | $LiBH_3NMe_2$ | 100 mL |
| FW 64.85 | | |

**Lithium morpholinoborohydride solution, 1 M in THF**

| | | |
|---|---|---|
| **65,830-8** | | 25 mL |
| $C_4H_{11}BLiNO$ | $LiBH_3NR_2$ ($NR_2$ = 4-morpholino) | 100 mL |
| FW 106.89 | | |

**Lithium pyrrolidinoborohydride solution, 1 M in THF**

| | | |
|---|---|---|
| **65,824-3** | | 25 mL |
| $C_4H_{11}BLiN$ | $LiBH_3NR_2$ ($NR_2$ = 1-pyrrolidino) | 100 mL |
| FW 90.89 | | |

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

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

# Recent Advances in the Chemistry of Lithium Aminoborohydrides†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*CTG Consulting, LLC*
*Midland, MI 48642, USA*


Dr. Christian T. Goralski

## Outline

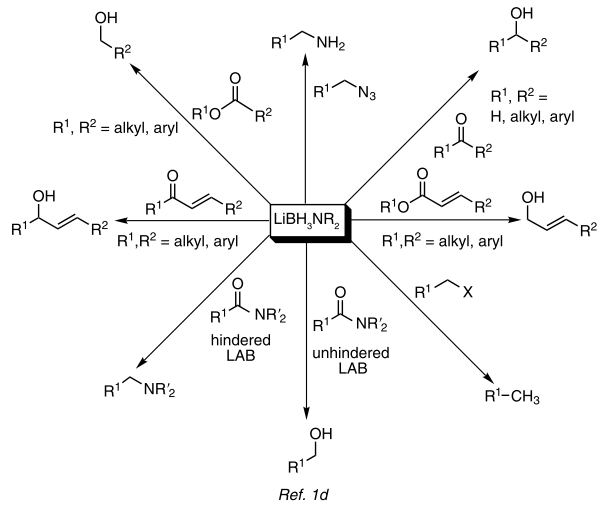


## 1. Introduction

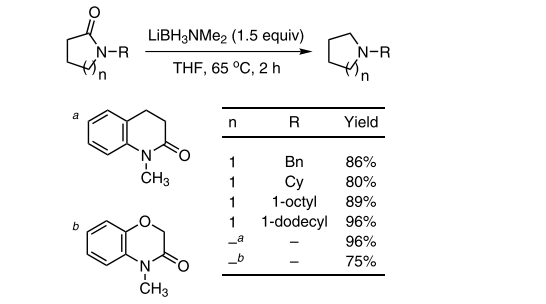
Lithium aminoborohydrides (LABs) are a new class of powerful, selective, and air-stable reducing agents. LABs can be prepared as solids or 1–2 M THF solutions, or can be generated in situ for immediate use.[1] Since LABs can be synthesized from any primary or secondary amine, the steric and electronic environments of these reagents can be easily controlled. Solid LAB reagents can be used in dry air as easily as sodium borohydride, and they maintain their chemical reactivity for at least 6 months when stored at 25 °C under nitrogen or dry air. THF solutions of LABs retain their chemical reactivity for at least 9 months when stored at 25 °C under nitrogen. LABs are capable of reducing a variety of functional groups (**Scheme 1**),[1d] and their use as reducing agents has been the subject of several reviews.[2] The present survey covers relevant research that has been published in the past five years.

## 2. Reduction of *N*-Alkyllactams and Amides

*N*-Alkyllactams are reduced with 1.5 equivalents of $LiBH_3NMe_2$ in THF at 65 °C in 2 hours, affording the corresponding cyclic amines in good-to-excellent yields (**eq 1**).[3] The method is general for both five- and six-membered *N*-alkyllactams. LAB reagents can perform a reagent-controlled reduction of amides to give either the corresponding alkanols or aminoalkanes. It is believed that, in sterically less demanding LABs, the boron moiety complexes the N-atom of the amide, making it a better leaving

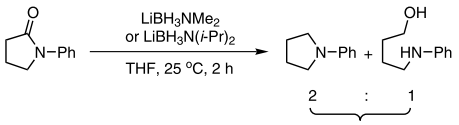



**Scheme 1**. Summary of the Reduction Reactions of LABs.

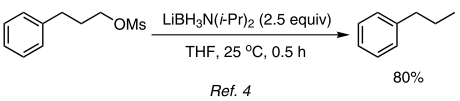



| n | R | Yield |
|---|---|---|
| 1 | Bn | 86% |
| 1 | Cy | 80% |
| 1 | 1-octyl | 89% |
| 1 | 1-dodecyl | 96% |
| –[a] | – | 96% |
| –[b] | – | 75% |

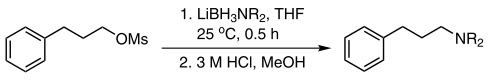
**eq 1**




**eq 2**



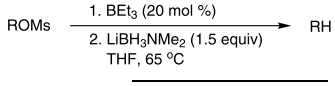

**eq 3**




| $NR_2$ | Yield |
|---|---|
| $NMe_2$ | 92% |
| $NEt_2$ | 75% |
| 1-pyrrolidino | 94% |
| 4-morpholino | 87% |
| 1-homopiperidino | 99% |

Ref. 4

**eq 4**




| R | Time | Yield |
|---|---|---|
| $Ph(CH_2)_3$ | 0.25 h | 94% |
| cyclohexyl | 4 h | 95% |

Ref. 4

**eq 5**

group. This leads to an aldehyde, which is reduced further to the primary alcohol. In the case of sterically more demanding LABs, an imine is formed as an intermediate, which is then reduced to the aminoalkane. For example, 1-pyrrolidinooctanamide can be reduced either to 1-octanol (71%) with $LiBH_3$(1-pyrrolidino) or 1-pyrrolidinooctane (95%) with the sterically bulky $LiBH_3N(i\text{-}Pr)_2$.[1c] Based on these observations, it was thought that lactams might behave similarly and lead to the corresponding cyclic amines or ring-opened amino alcohols. Unfortunately, only 1-phenyl-2-pyrrolidinone gave any ring-opened product with either $LiBH_3NMe_2$ or $LiBH_3N(i\text{-}Pr)_2$ (**eq 2**).[3]

## 3. Reduction of Primary Alkyl Sulfonates to Hydrocarbons

Primary alkyl sulfonates undergo facile reduction to the corresponding hydrocarbons with sterically hindered LABs (**eq 3**).[4] Unfortunately, a sterically hindered LAB reagent will not reduce secondary alkyl sulfonates, which are recovered unchanged even after prolonged exposure at reflux temperature. For example, cyclohexyl methanesulfonate was completely recovered after treatment with 2.5 equivalents of $LiBH_3N(i\text{-}Pr)_2$ in THF at 65 °C for 5 days.[4]

## 4. Conversion of Primary Alkyl Methanesulfonates to Amines

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

The reduction of alkyl methanesulfonates with unhindered LAB reagents is possible, however, in the presence of $Et_3B$. Under these reaction conditions, $LiBHEt_3$ is generated in situ. Using 1.5 equiv of $LiBH_3NMe_2$ and 20 mol % of $Et_3B$, the reduction of both primary and secondary alkyl mesylates is accomplished in very high yields (**eq 5**).[4]

## 5. Tandem Amination–Reduction Reactions

The reaction of LABs with benzonitriles containing ring halogens has provided some very interesting results. Treatment of 2-chlorobenzonitrile with $LiBH_3NMe_2$ in refluxing THF afforded a 90% isolated yield of a 70:30 mixture of 2-(dimethylamino)-benzylamine (the product of nucleophilic aromatic substitution of the chlorine by the dimethylamino group—another example of nitrogen transfer—followed by reduction of the cyano group) and 2-chlorobenzylamine (**Scheme 2**).[5,6] Reaction of 2-chlorobenzonitrile with lithium pyrrolidinoborohydride under similar conditions gave analogous results: a 70:30 mixture of 2-(pyrrolidino)benzylamine and 2-chlorobenzylamine. Treatment of 2-chlorobenzonitrile with pyrrolidine under similar conditions gave only recovered starting material.

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

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

## 6. Synthesis of 2-(Dialkylamino)pyridines

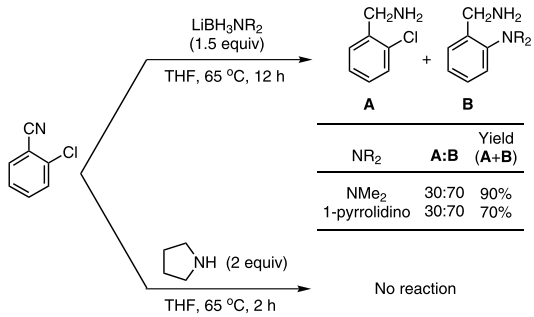
Aminopyridines are attractive synthetic targets, since many are biologically active molecules. For example, several aminopyridine-based pharmaceuticals are used to treat a range of disorders.[7a–e] In addition, and because of their chelating properties, aminopyridines are commonly used as ligands in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

We have extended the amination capabilities of LABs to 2-fluoropyridine. The direct amination of 2-fluoropyridine with LABs was first attempted to determine if an amination reaction analogous to that of 2-fluorobenzonitrile was indeed possible. The same reaction conditions that had been optimized for the amination of 2-fluorobenzonitrile were employed. Upon addition of 2-fluoropyridine to a THF solution of $LiBH_3NMe_2$, the colorless solution turned deep red in color. Meisenheimer complexes, the anionic intermediates formed during an $S_NAr$ reaction, are known to form highly colored solutions. In fact, a similar deep-red color change in the $S_NAr$ reactions of LABs with 2-halobenzonitriles had been observed. Gratifyingly, 2-(dimethylamino)pyridine was isolated in 59% yield. After these initial findings, attempts were made to optimize the reaction conditions. We discovered that elevated reaction temperatures were unnecessary and only 1.1 equiv of LAB reagent was required for the desired transformation. When 2-fluoropyridine was reacted at room temperature with 1.1 equiv of lithium homopiperidinoborohydride in THF for 1 h, 2-(homopiperidino)pyridine was isolated in 97% yield after employing the modified workup procedure. The products of the reaction of various LAB reagents with 2-fluoropyridine are shown in **equation 7**.[8] The optically active LAB reagent prepared from (*S*)-(+)-2-methylpiperidine gave the lowest yield (60%), presumably as a result of increased steric requirements. 2-Chloropyridine reacted similarly with $LiBH_3NMe_2$ (THF, 65 °C, 1 h) and led to 2-dimethylaminopyridine in 87% yield.[8]

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

Our investigations of the possible mechanism of the reaction of 2-fluoropyridine with LABs led us to hypothesize that the pyridine could be activated by coordination to boron during the reaction.[10] To test this hypothesis, we treated 2-fluoropyridine with $BH_3$•$SMe_2$ to form a 2-fluoropyridine–borane complex. We then reacted the complex with $LiNPr_2$ (formed from dipropylamine and *n*-BuLi) at 0 °C; 2-dipropylaminopyridine was isolated from this reaction in 50% yield (**Scheme 5**).[10]

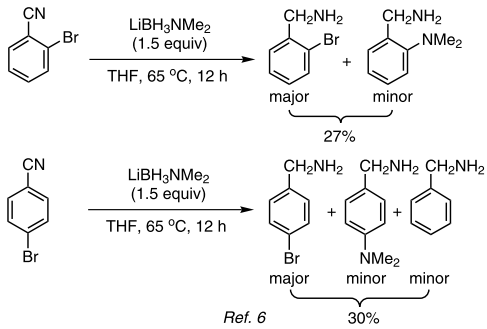
This unexpected result led us to investigate the importance of pre-activating 2-fluoropyridine with $BH_3$. When 2-fluoropyridine




| $NR_2$ | A:B | Yield (A+B) |
|---|---|---|
| $NMe_2$ | 30:70 | 90% |
| 1-pyrrolidino | 30:70 | 70% |

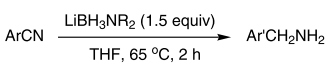
*Ref. 5a,6*

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




*Ref. 6*

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

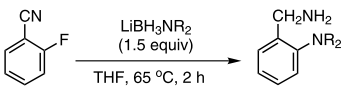



| Ar | Ar' | Yield |
|---|---|---|
| 2-$FC_6H_4$ | 2-$R_2NC_6H_4$ | 84% |
| 4-$FC_6H_4$ | 4-$R_2NC_6H_4$ | 89% |

$NR_2$ = 1-pyrrolidino

*Ref. 6*

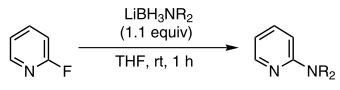
**Scheme 4**. Tandem Amination–Reduction of 2- and 4-Fluorobenzonitriles.




| $NR_2$ | Yield |
|---|---|
| $NMe_2$ | 81% |
| $NEt_2$ | 70% |
| 1-pyrrolidino | 84% |
| 1-piperidino | 94% |
| 4-morpholino | 81% |
| 1-homopiperidino | 75% |

*Ref. 6*

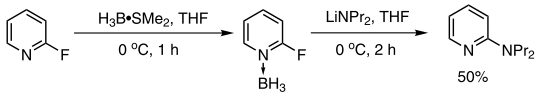
**eq 6**




| $NR_2$ | Yield |
|---|---|
| $NMe_2$ | 85% |
| $NEt_2$ | 76% |
| $NPr_2$ | 75% |
| 1-pyrrolidino | 81% |
| 1-piperidino | 99% |
| 4-morpholino | 83% |
| 1-homopiperidino | 97% |
| NMeBn | 95% |
| (*S*)-2-methyl-1-piperidino | 60% |

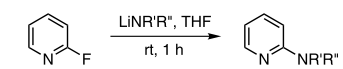
*Ref. 8*

**eq 7**

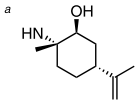



*Ref. 10*

**Scheme 5**. Activation of 2-Fluoropyridine with $H_3B{\bullet}SMe_2$.

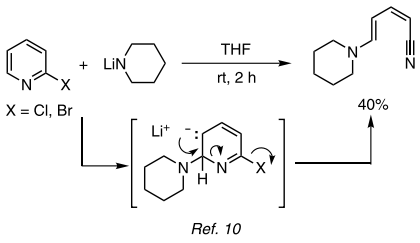



| NR'R" | Yield |
|---|---|
| 1-pyrrolidino | 80% |
| 1-piperidino | 82% |
| 4-morpholino | 85% |
| 1-homopiperidino | 83% |
| NHCy | 40% |
| $NEt_2$ | 64% |
| NMeBn | 82% |
| NH[(*R*)-MeCHPh] | 64% |
| –[a] | 10% |

[a] 

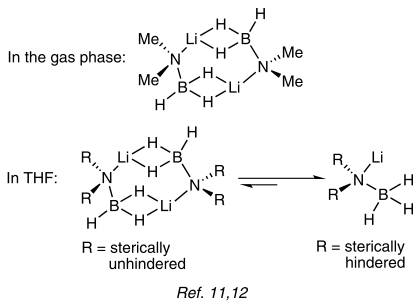

*Ref. 10*

**eq 8**




*Ref. 10*

**eq 9**




*Ref. 11,12*

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

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

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

## 7. Theoretical Calculations on LABs

Theoretical calculations of the equilibrium geometries and energies of LABs, carried out by Pratt and co-workers, indicate that $LiBH_3NMe_2$ exists largely as a hydrogen-bridged dimer in both the gas phase and as the bis(dimethyl ether) microsolvate (**Figure 1**).[11] More recently, this group utilized Density Functional Theory (DFT) calculations to determine the effects of ethereal solvents on the aggregation state of $LiBH_3NMe_2$. The calculations suggest that the dimer might coexist with the monomer in tetrahydrofuran. More hindered lithium dialkylaminoborohydrides exist primarily as monomers in ethereal solutions.[12] The kinetics (pseudo-first order in 1-chlorodecane) of the amination of 1-chlorodecane with $LiBH_3NMe_2$ (THF, 25 °C) showed no detectable change in reaction rate with time, suggesting that $LiBH_3NMe_2$ exists primarily as a monomer in THF, although the possibility of monomer–dimer equilibration cannot be ruled out.

## 8. Conclusions

Lithium aminoborohydrides are a new class of powerful yet selective reducing agents that reproduce, in air, virtually all of the transformations for which $LiAlH_4$ is now used. The reactivity of LABs is comparable to that of both $LiAlH_4$ and Vitride®. LABs are air-stable, nonpyrophoric, thermally stable, and liberate hydrogen only slowly in protic solvents above pH 4. LABs, whether solid or as THF solutions, retain their chemical activity for at least 6 months when stored under nitrogen at 25 °C. LABs can be synthesized from any primary or secondary amine, thus allowing precise control of the steric and electronic environments of these reagents.

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

In undergraduate teaching laboratories, transformations that would seldom be attempted because of the need to use $LiAlH_4$ or borane—such as the reduction of tertiary amides or esters—may become routine experiments with the use of LABs. For example, for the past four years, students at the University of California, Santa Cruz, who have taken the introductory organic chemistry laboratory class, have employed 1 M THF solutions of LABs to reduce aliphatic, aromatic, and α,β-unsaturated esters to the corresponding aliphatic, aromatic, and allylic alcohols, in air, in 70–98% isolated yields without incident or difficulty. In academic research laboratories, the short reaction time, ease of generation and handling, and simple workup procedure of reductions with

LABs make these new reagents attractive alternatives to $LiAlH_4$ or $LiAlHEt_3$ (Super-Hydride®) reductions.

## 9. Acknowledgements

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

## 10. References and Notes

(†) Dedicated to Professor Herbert C. Brown, who passed away on December 19, 2004.

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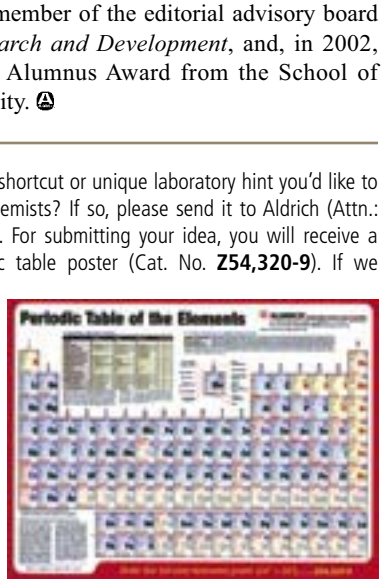


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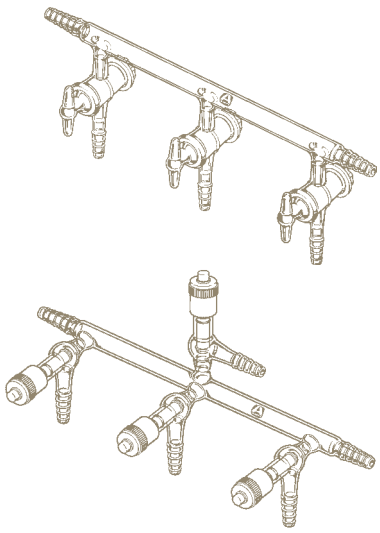
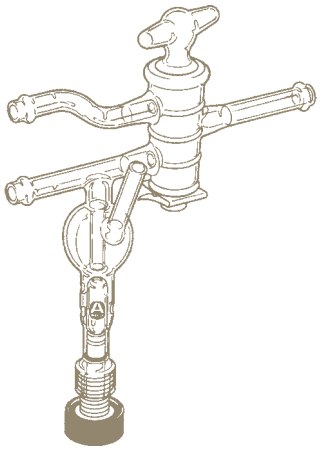


| No. of Positions | Overall L (mm) | Glass Stopcocks Cat. No. | High-Vacuum PTFE Valves Cat. No. |
|---|---|---|---|
| **Standard manifold** | | | |
| 3 | 300 | **Z53,213-4** | **Z53,219-3** |
| 4 | 400 | **Z53,214-2** | **Z53,220-7** |
| 5 | 500 | **Z53,215-0** | **Z53,221-5** |
| **Manifold with vacuum-gauge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



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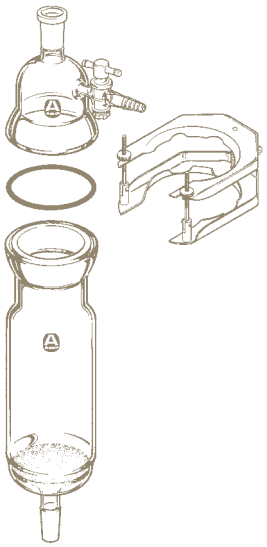

| Cap. (L) | Frit Diam. (mm) | Diam. × H[a] (mm) | ⧩24/40 Cat. No. | ⧩29/32 Cat. No. |
|---|---|---|---|---|
| 1 | 90 | 95 × 340 | **Z51,728-3** | **Z51,734-8** |
| 2 | 120 | 130 × 360 | **Z51,729-1** | **Z51,735-6** |
| 4 | 150 | 165 × 420 | **Z51,730-5** | **Z51,736-4** |
| 6 | 150 | 165 × 540 | **Z51,731-3**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

[a] Dimensions of bottle.

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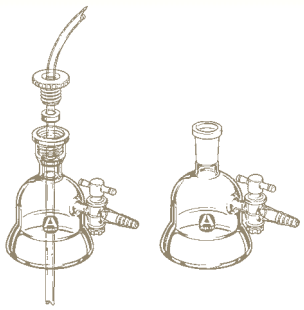
**Standard taper**—The ⧩24/40 and ⧩29/32 joints can accommodate a transfer adapter or a filter funnel.



| Description | Cat. No. |
|---|---|
| Torion™ inlet top | **Z51,712-7** |
| ⧩24/40 top | **Z51,713-5** |
| ⧩29/32 top | **Z51,739-9** |
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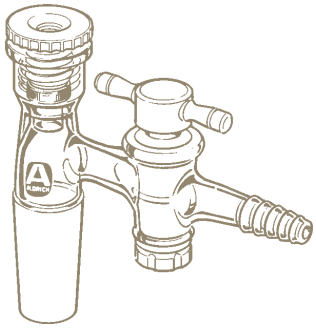

| Tubing O.D. (in.) | Inner ⧩Joint | PTFE Stopcock Cat. No. | Glass Stopcock Cat. No. |
|---|---|---|---|
| 3/16 | 14/20 | **Z53,183-9** | **Z53,195-2** |
| 3/16 | 19/22 | **Z53,184-7** | **Z53,196-0** |
| 5/16 | 14/20 | **Z53,185-5** | **Z53,197-9** |
| 5/16 | 19/22 | **Z53,186-3** | **Z53,198-7** |
| 5/16 | 24/40 | **Z53,187-1** | **Z53,199-5** |
| 5/16 | 29/32 | **Z53,189-8** | **Z53,200-2** |
| ½ | 24/40 | **Z53,190-1** | **Z53,201-0** |
| ½ | 29/32 | **Z53,192-8** | **Z53,202-9** |
| ½ | 34/45 | **Z53,193-6** | **Z53,203-7** |
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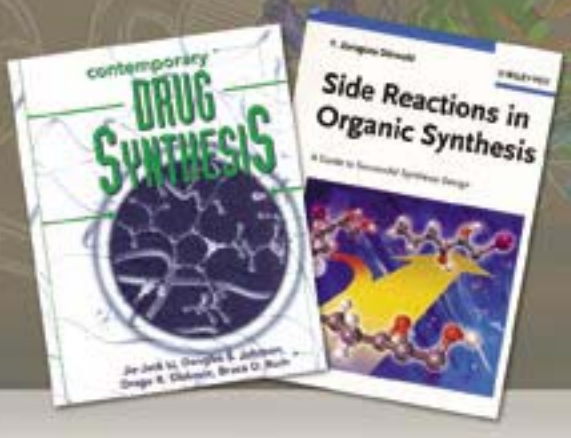


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THE NEGISHI COUPLING: AN UPDATE

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VOL. 38, NO. 3 • 2005

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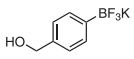
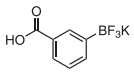
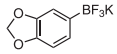
**659762**  1 g, 5 g

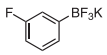
### Potassium 3-carboxyphenyltrifluoroborate

**659789**  1 g, 5 g

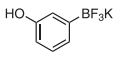
### Potassium 3,4-(methylenedioxy)phenyltrifluoroborate

**659754**  1 g, 5 g

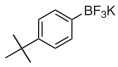
### Potassium 3-fluorophenyltrifluoroborate

**659770**  1 g, 5 g

### Potassium 3-hydroxyphenyltrifluoroborate

**659746**  1 g, 5 g

### Potassium 4-*tert*-butylphenyltrifluoroborate, 95%

**654728**  1 g, 10 g

### Potassium 2-methoxyphenyltrifluoroborate

**654930**  1 g, 5 g

### Potassium vinyltrifluoroborate, 95%

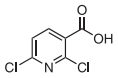
**655228**  1 g, 5 g

Trifluoroborates are air-stable alternatives to boronic acids in the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction.[1–3] They are more robust, easier to handle, and less prone to protodeboronation.[1] They display a remarkably uniform behavior.[2]

(1) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302. (2) Molander, G. A. et al. *J. Org. Chem.* **2003**, *68*, 5534. (3) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49.

## BUILDING BLOCKS

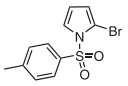
### 2,6-Dichloronicotinic acid, 97%

**658219**  1 g, 5 g

This pharmaceutical research[1,2] key building block is now available in 97% purity. See **479586** for a technical grade (90%) of this material.

(1) Kelly, T. P. et al. *J. Labelled Compd. Radiopharm.* **2001**, *44*, 451. (2) Laeckmann, D. et al. *Bioorg. Med. Chem.* **2002**, *10*, 1793.

### 2-Bromo-1-(*p*-toluenesulfonyl)pyrrole, 90%

**650900**  1 g, 5 g

This product is a stable and easily handled alternative for the labile bromopyrrole, and is an excellent substrate for the Suzuki coupling reaction. The tosyl group is readily cleaved under basic conditions to generate the 2-arylpyrrole coupling product.

Knight, L. W. et al. *Synlett* **2003**, 1993.

### *N*-Boc-piperidine, 98%

**655872**  5 g, 25 g

A wide variety of substituted piperidines can be synthesized from this Boc-protected building block. Lithiation with BuLi leads to substitution at the 2 position with aryl, vinyl, and alkynyl halides.[1] Its use in the stereoselective synthesis of D-*threo*-methylphenidate (Ritalin®) and similar substrates has been reported.[2,3]

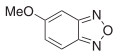
(1) Dieter, R. K.; Li, S. J. *J. Org. Chem.* **1997**, *62*, 7726. (2) Axten, J. M. et al. *J. Am. Chem. Soc.* **1999**, *121*, 6511. (3) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.

## BENZOFURAZANS

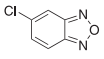
### Benzofurazan, 97%

**650137**  1 g, 10 g

### 5-Methoxybenzofurazan, 97%

**656925**  1 g, 5 g

### 5-Chlorobenzofurazan

**659118**  1 g, 5 g

Benzofurazans have been utilized as effective fluorescence probe motifs[1] and as medicinal building blocks in the synthesis of antileukemic agents.[2,3]

(1) Uchiyama, S. et al. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2525. (2) Ghosh, P. B.; Whitehouse, M. W. *J. Med. Chem.* **1968**, *11*, 305. (3) Ghosh, P. B.; Whitehouse, M. W. *J. Med. Chem.* **1969**, *12*, 505.

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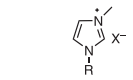
(1) Seddon, K. R.; Stark, A. *Green Chem.* **2002**, *4*, 119. (2) Dyson, P. J.; Ellis, D. J.; Parker, D. G.; Welton, T. *Chem. Commun.* **1999**, 25. (3) *Ionic Liquids in Synthesis*; Wasserscheid, P., Welton, T., Eds.; Wiley-VCH, 2003; p 26. (4) Stark, A.; Ajam, M.; Green, M.; Raubenheimer, H. G.; Ranwell, A.; Ondruschka, B. *Adv. Synth. Catal.*, submitted for publication, 2005.

R = Bu, Et; X = Cl, $PF_6$, $BF_4$

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| **39931** | **1-Butyl-3-methylimidazolium tetrafluoroborate**, for catalysis, ≥98.5% (T) | 5 g<br>50 g |
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## ABOUT OUR COVER

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

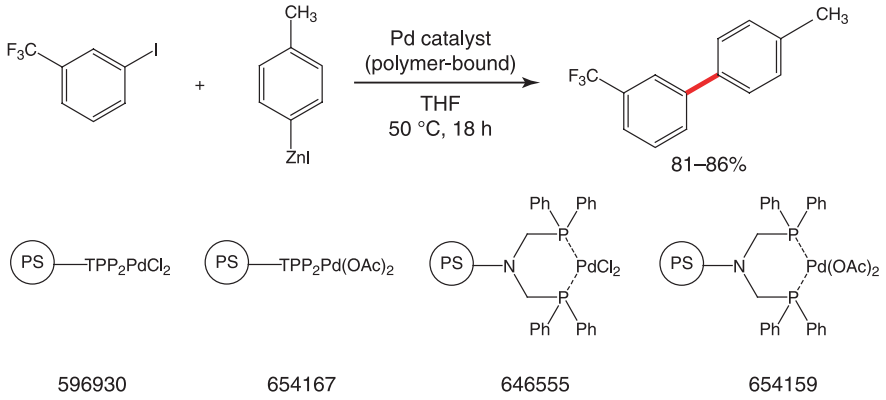
*Valdemosa, Majorca: Thistles and Herbage on a Hillside* (oil on canvas, 55.8 × 71.1 cm) was painted by the artist John Singer Sargent in 1908. Sargent was born in 1856 in Florence, Italy, to expatriate American parents. His first artistic training was in Rome, but he later attended the Accademia delle Belle Arti in Florence, and studied drawing at the École des Beaux-Arts and painting in the studio of the portrait painter Charles Carolus-Duran in Paris. In 1877, he began to exhibit in the Salons, the French government sanctioned art exhibitions. Sargent copied works by Diego Velázquez on a trip to Spain in 1879 and by Frans Hals in Belgium and Holland in 1880, an experience that had a great impact on his artistic development.

By the end of the nineteenth century, Sargent had become the most sought-after portrait painter of his time, but he always felt constrained by the limitations of portrait painting. By the early twentieth century, his success finally allowed him to free himself almost completely from the painting of formal portraits. He made annual trips to Spain, Italy, Austria, and Switzerland, and it was on a trip to the Balearic island of Majorca that he painted this small picture. He had no interest in what he called "enormous views and huge skies", and chose to concentrate on a small patch of vegetation growing in the earth of a hillside. This painting is not strictly a realistic image, but one which, with its strong formal contrasts, bright colors, and seemingly spontaneous execution, achieves an extraordinary intensity of expression. Confronted with such an immediate response to nature that seems almost spiritual in its intensity, it is easy to understand Sargent's disdain for the artificiality of the academic portrait painting that had dominated his career for most of his life.

**This painting was acquired by the National Gallery of Art, Washington, DC, through the Avalon Fund and by Gift of Virginia Bailey Brown.**

# The Negishi Coupling Catalyzed by Palladium on Polymer Supports

Supported palladium catalysts are widely used in the Suzuki, Heck, and Sonogashira cross-coupling reactions. However, no examples of their use in the Negishi coupling have been reported in the literature. There are several advantages to using supported catalysts in organic synthesis. These include reagent stability, suitability for automation, ease of workup, recyclability, and lower Pd contamination in the final product. Herein, we describe the application of four commercially available polymer-supported palladium reagents as catalysts in the Negishi coupling.




## Typical Experimental Procedure

The palladium catalyst (0.01 mmol Pd) is charged into the reaction vessel. 3-Iodobenzotrifluoride (144 µL, 1 mmol) is then introduced, followed by addition of a THF solution of 4-methylphenylzinc iodide (0.5 M, 3 mL, 1.5 mmol). The resulting mixture is stirred at 50 °C for 18 h, cooled, and then filtered. The resin is washed with THF (2 × 3 mL), the THF filtrates combined and evaporated. The evaporation residue is dissolved in a minimum amount of THF and filtered through a silica gel pad to remove any residual zinc compounds. The pad is rinsed with ether, and the combined ether filtrates evaporated. The crude product thus obtained is purified by flash chromatography on silica gel (column size 1.5 × 2.5 cm) using hexane as eluent. The purified product, 4-methyl-3′-trifluoromethylbiphenyl, is isolated as a colorless oil. (See the table below for yields.)

| Cat. No. | Catalyst Name | Product Yield | Byproduct Yield[a] |
|---|---|---|---|
| **596930-1G**<br>**596930-5G** | Dichlorobis(triphenylphosphine)palladium(II), polymer-bound | 83% | 4% |
| **654167-5G**<br>**654167-25G** | Diacetoxybis(triphenylphosphine)palladium(II), polymer-bound | 84% | 5% |
| **646555-1G**<br>**646555-5G** | Bis[(diphenylphosphanyl)methyl]aminepalladium(II) dichloride, polymer-bound | 86% | 4% |
| **654159-1G**<br>**654159-5G** | Bis[(diphenylphosphanyl)methyl]aminepalladium(II) diacetate, polymer-bound | 81% | 5% |

[a] 4,4′-Dimethylbiphenyl.

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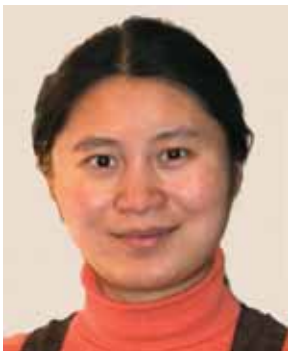
# Palladium-Catalyzed Alkenylation by the Negishi Coupling


Professor Ei-ichi Negishi


Ms. Qian Hu

*Ei-ichi Negishi,* Qian Hu, Zhihong Huang, Mingxing Qian, Guangwei Wang*
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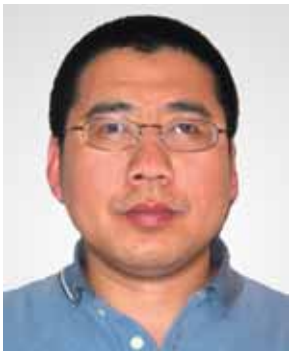

Dr. Mingxing Qian


Mr. Guangwei Wang

## Outline

## 1. Introduction

The palladium-catalyzed cross-coupling of an organometal ($R^1M$) with an organic electrophile ($R^2X$) has emerged over the past thirty years as one of the most general and selective methods for carbon–carbon-bond formation (**eq 1**). Currently, it appears to be generally superior to related methods involving the use of Ni, Cu, or Fe catalysts in its scope and stereo-, regio-, and chemoselectivities.[1] The $R^1$ group of $R^1M$ can be aryl, alkenyl, alkynyl, allyl, benzyl, propargyl, alkyl, cyano, or enoxy; while the $R^2$ group of $R^2X$ can be aryl, alkenyl, alkynyl, allyl, benzyl, propargyl, alkyl, or acyl. Use of other related carbon groups as $R^1$ and/or $R^2$ is not only conceivable, but also known in the literature. Even if only those nine types of organometals ($R^1M$) and eight types of organic electrophiles ($R^2X$) mentioned above are considered, their binary combinations lead to 72 different types of cross-coupling reactions, and most of these reactions have indeed been developed. Until recently, the use of alkyl electrophiles lacking proximal π bonds had been considered to be categorically very difficult, and the task of Pd-catalyzed alkylation had been achieved by using alkylmetals. The latter is still of much broader synthetic applicability. However, some recent developments suggest that this generalization may have to be significantly modified in the future, as discussed in Section 2.6. Another group of categorically difficult Pd-catalyzed cross-coupling reactions are those involving cross-coupling between allyl, benzyl, and/or propargyl groups.[1a] In addition, a more promising, direct, and selective α alkenylation and α alkynylation of metal enolates[1a,2–4] need to be further developed.

The Pd-catalyzed cross-coupling can be performed with organometals containing any of ten or more different metals including Zn, Al, or Zr (Negishi coupling),[1] B (Suzuki coupling),[1,5,6] Sn (Stille coupling),[1,7] as well as Li,[8] Mg,[9,10] In,[11] Si,[1,12] Cu,[13] and Mn.[14] This review will briefly discuss the Pd-catalyzed alkenylation involving Zn-, Al-, or Zr-containing organometals and leading to the direct formation of a carbon–carbon single bond to alkenyl groups. Its application to the synthesis of alkenes of biological, medicinal, and materials science interest will also be briefly discussed. To indicate various types of cross-coupling, compound adjectives, such as alkenyl–aryl and aryl–alkenyl, are used. In these words, the first and second terms indicate the $R^1$ and $R^2$ groups of $R^1M$ and $R^2X$, respectively. Recent advances in the development of (i) hydrometallation–cross-coupling and carbometallation–cross-coupling tandem processes, and (ii) the selective disubstitution of 1,1- and 1,2-dihaloalkenes will be emphasized. The Pd-catalyzed alkenylation via cross-coupling may be classified into 16 types. Most of these types and results that had been reported prior to 1998 have been comprehensively reviewed elsewhere.[1a] It is worth mentioning, however, that two recent reviews of the Pd-catalyzed alkynylation[1,15] contain many new examples of the Pd-catalyzed alkynyl–alkenyl coupling.

$$R^1M + R^2X \xrightarrow{PdL_n(cat.)} R^1{-}R^2 + MX \qquad \textbf{eq 1}$$

## 2. The Pd-Catalyzed Alkenylation with Zn, Al, and Zr Organometals

### *2.1. Early Findings*

Between 1976 and 1978, Negishi's group published close to ten seminal papers on the Pd- or Ni-catalyzed cross-coupling,[16–24] disclosing, for the first time, the following findings pertinent to this review.

i. The Pd- or Ni-catalyzed reaction of alkenylalanes with aryl halides represents the first set of examples of the Pd- or Ni-catalyzed organoalane cross-coupling, and of the Pd- or Ni-catalyzed hydrometallation–cross-coupling tandem reaction.[16]
ii. The alkenyl–alkenyl couplings of *cis*- or *trans*-1-iodo-1-hexene with *trans*-1-(diisobutylalumino)-1-hexene represent the earliest examples of the Pd- or Ni-catalyzed "pair-selective" and stereoselective synthesis of conjugated dienes.[17]
iii. These reactions also demonstrated, for the first time, some distinct advantages of Pd over Ni, e.g., superior stereospecificity: ≥98% (Pd) vs ≥90% (Ni).[17]
iv. The reaction of (*E*)-3-bromo-2-methylacrylic ester provided the first example of generally favorable Pd-catalyzed conjugate substitution.[17,18,22–25]
v. The Pd-catalyzed reaction of alkynylzinc chlorides with alkenyl halides[18]—along with the related alkynyl–aryl,[19] aryl–aryl,[20] and benzyl–aryl[20] coupling reactions—not only provided some of the earliest examples of the Pd-catalyzed cross-coupling of organozincs, but also indicated the superior reactivity of organozincs under the Pd-catalyzed cross-coupling conditions relative to the ten or so other types of organometals mentioned earlier.
vi. Following the discovery of the Ni-catalyzed cross-coupling reaction of alkenylzirconiums with aryl halides in 1977,[21] the Pd-catalyzed alkenyl–alkenyl coupling of alkenylzirconium derivatives with alkenyl halides was reported in 1978.[22]
vii. The first examples of the Pd-catalyzed carboalumination–cross-coupling tandem reaction were also reported in 1978.[23] The use of Zn salts, such as $ZnCl_2$ or $ZnBr_2$, as additives or cocatalysts in the coupling step of this tandem reaction was shown to be highly desirable or even essential to observing satisfactory results. This study demonstrated, for the first time, the concept of double metal catalysis and the favorable effects of additives on the Pd- or Ni-catalyzed cross-coupling.[23]
viii. The findings reported in references 16–23 established that the Pd- or Ni-catalyzed cross-coupling can be achieved with organometals containing various metal countercations other than Mg, which had previously been used almost exclusively. A systematic screening of metal countercations was conducted for the first time for the Pd-catalyzed reaction of alkynylmetals with *o*-tolyl iodide.[24–26] This study indicated that, in addition to alkynylzincs, organometals containing B and Sn were superior reagents, and these were subsequently developed as the Suzuki[1,5,6] and Stille[1,7] coupling reactions, respectively. The reaction of *n*-PentC≡CB(*n*-Bu)$_3$Li with *o*-tolyl iodide, producing the desired *n*-PentC≡C(*o*-Tol) in

92% yield, was the first example of the Pd-catalyzed cross-coupling of organoboron compounds. Further details of the early developments of the Negishi coupling and related cross-coupling reactions are discussed in the pertinent reviews.[25,26]

## 2.2. Summary of Current Status

### 2.2.1. Metal Countercations

The Pd-catalyzed cross-coupling has proved to be of wide scope with respect to metal countercations.[1] In many less demanding cases, all or most of the ten or more metals that have been used as countercations may work satisfactorily. In other more demanding cases, however, critical differences among them have been observed. It is therefore desirable to be familiar with the pros and cons of the various available countercations. In view of the multimechanistic and multifaceted nature of the Pd-catalyzed cross-coupling, however, it is not practical to compare and rank them on one scale. From a practical viewpoint, synthetic chemists are generally seeking those methods and reactions that satisfy some or most, if not all, of the following criteria: (i) predictably general applicability, especially with respect to the $R^1$ and $R^2$ groups to be coupled, (ii) high product yield, (iii) high regio-, stereo-, and chemoselectivities minimizing the need for separation and purification, (iv) high efficiency including step-economy as well as operational simplicity and convenience, (v) low costs of reagents, catalysts, other materials, and of other aspects of operation, and (vi) high level of safety especially with regards to toxicity as well as explosion and fire hazards.

A priori, organometals containing highly electropositive metals, such as Li and Mg, which are normally considered to be "highly nucleophilic", would be desirable from a reactivity point of view. Conversely, organometals containing highly electronegative metalloids, such as B and Si, might be expected to be of limited reactivity. Under conditions that are stoichiometric in Pd, highly electropositive metals, such as Li and Mg, are at least as reactive as Zn.[27] Under Pd-catalyzed conditions, however, the reactivity order of Zn > Mg >> Li has been observed more often than not.[1,24,27,28] This unexpected order of reactivity has been tentatively interpreted in terms of catalyst poisoning by highly nucleophilic organometals containing Li and Mg. On the other hand, there have also been indications that Grignard reagents display a significantly higher catalytic reactivity than the corresponding organozincs in some cases, such as those involving organic chlorides.[29] Therefore, in cases where Grignard reagents and organolithiums are generated first, they should also be tested in the cross-coupling reaction before converting them into other organometals.

At the end of the nucleophilicity scale lie highly electronegative metals and metalloids, such as B and Si. Organoboranes, as opposed to borates, and organosilanes are as such of very low reactivities at best. In fact, silyl groups are often used as protecting groups. As noted in the first successful Pd-catalyzed organoboron cross-coupling[24–26] vis-à-vis earlier failures with alkenylboranes,[16,17] the reactivity of organoboranes can be substantially increased through ate complexation.[1,5,6] Similar activations of organosilanes with fluorides have also made organosilanes useful in the Pd-catalyzed cross-coupling.[12] Generally speaking, however, it has become increasingly clear that Zn displays the highest reactivity under the Pd-catalyzed conditions, and that its catalytic reactivity is followed by those of several metals of intermediate electronegativity including Al,[16,17,25] In,[11] Sn,[30–32] Zr,[33] and Cu[34] (**Scheme 1**).[1a] Thus, one can expect that high reactivity with respect to the desired cross-coupling—relative to other undesired processes including regio- and stereoisomerizations and catalyst poisoning—should lead to high product yields, a wider scope of cross-coupling, higher selectivities, higher catalyst turnover numbers, and lower cost of operation.

The selection of metal countercations, of course, involves some other factors, such as chemoselectivity, operational convenience including compatibility with water and air, economy, safety, and others. Some of these factors must undoubtedly be responsible for the current widespread use of B and Sn. For toxicity related reasons, however, the use of Sn might be projected to be increasingly limited. On the other hand, it appears that Si might be used more extensively in the future. Along a more scientific line, the facile and convenient preparation of stereo- and regio-defined alkenylmetals and the corresponding halides or related electrophiles is one of the most critical factors in selecting countercations for the Pd-catalyzed alkenylation. Several metals and metalloids such as B, Al, In, Zr, Cu, Si, Sn, and Zn have been used for forming the first-generation alkenylmetals directly from alkynes, rendering these metals attractive countercations in Pd-catalyzed alkenylations.[5,6,34–47] On the other hand, alkenylmetals containing Li and Mg have been prepared mostly from alkenyl halides rather than alkynes. In many cases, the methods of converting alkynes to alkenylmetals are also applicable to the preparation of alkylmetals from alkenes.[48–50] Various types of hydrometallation, carbometallation, and heterometallation including metallometallation have been employed for the Pd-catalyzed alkenylation often in conjunction with the use of Zn or In salts as cocatalysts.

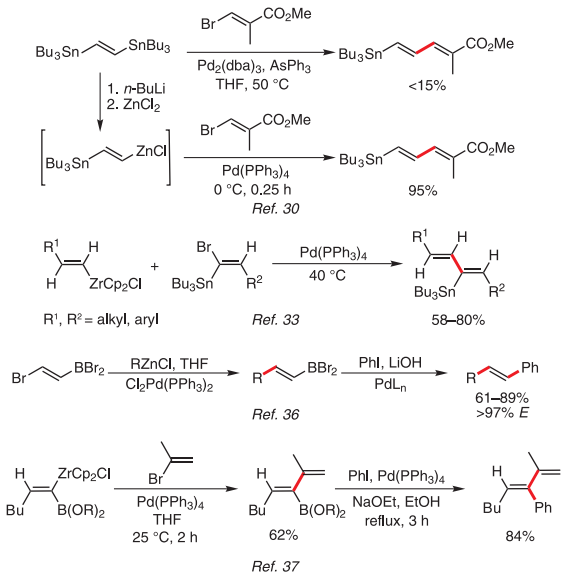
### 2.2.2. Leaving Groups

Other parameters influencing the Pd-catalyzed alkenylation reaction include the nature of the leaving group (X) in the electrophilic partner ($R^2X$), the Pd catalyst, cocatalyst or other additive, and solvent. In cases where $R^2X$ represents alkenyl electrophiles, the X group is usually I, Br, Cl, or some oxygen-containing group, such as OTf and $OPO(OR)_2$. For a given $R^2$ group, the generally observed order of reactivity of halogens is I > Br > Cl. Unfortunately, the generally least expensive, and hence most desirable, Cl-containing electrophile is the least reactive. Therefore, a reasonable course of action might be to choose first the most reactive I- or Br-containing electrophile and see if the desired cross-coupling can be satisfactorily achieved. If the coupling reaction is thus achievable, one may then attempt to use the less expensive Cl or other leaving groups. In this context, a recent report of the reactions of aryl and alkenyl chlorides with aryl- and alkynylzinc chlorides in THF–NMP at 100 °C in the presence of 2 mol % of $Pd[(t\text{-}Bu)_3P]_2$ is noteworthy.[51b]

### 2.2.3. Pd Catalysts, Cocatalysts or Other Additives, and Solvents

Three other chemical parameters are available for optimizing the reaction conditions: (i) phosphines and other ligands in the Pd catalysts, (ii) cocatalysts and other additives, and (iii) the solvents used. In recent years, some significant advances have been made in the first two categories, especially in ligands. These topics have very recently been discussed in some detail.[1b] Ligands, additives, and solvents specifically utilized in the Pd-catalyzed alkenylation with Zn, Al, and Zr organometals are presented in **Figure 1**.[51–60]

In summary, the selection of an optimal set of parameters for a given Pd-catalyzed cross-coupling is becoming increasingly more involved and at times confusing. Until recently, the combination indicated as *Procedure I (Conventional Standard Conditions)* and employing $PPh_3$ as the ligand, had been most widely utilized (**Figure 2**). In many less demanding cases, it has worked satisfactorily, and it should still be one of the first-round options.




**Scheme 1**. The Higher Reactivities Displayed by Zn and Zr Relative to Other Metals in the Pd-Catalyzed Alkenylation.

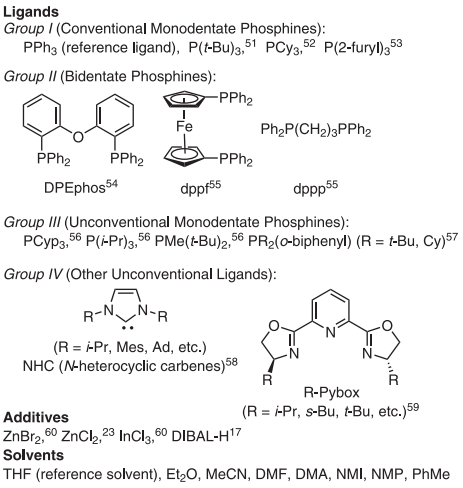



**Figure 1**. Ligands, Additives, and Solvents Commonly Used in the Pd-Catalyzed Alkenylation with Zn, Al, and Zr Organometals.

**Procedure I** (Conventional Standard Conditions):
*Catalyst*: 1–5 mol % of $Pd(PPh_3)_4$, or several variants of $Pd(PPh_3)_2L_n$ including $Cl_2Pd(PPh_3)_2$ with or without DIBAL-H; $Pd_2(dba)_3$ or $Pd(dba)_2$; $Cl_2Pd(MeCN)_2$; and $Li_2PdCl_4$ in the presence of $PPh_3$

*Additive*: $ZnBr_2$ or $ZnCl_2$, as needed
*Solvent*: THF and/or DMF

**Procedure II** (Modern Standard Conditions):
*Catalyst*: $Cl_2Pd$(DPEphos), $Cl_2Pd$(dppf), or $Cl_2Pd$(dppp)

*Catalyst Loading:* Initial screening at 1–5 mol % then consider $\leq 10^{-1}$–$10^{-3}$ mol %

*Additive*: $ZnBr_2$, $ZnCl_2$, or $InCl_3$, as needed
*Solvent*: THF and/or DMF

**Figure 2**. Conventional and Modern Standard Conditions for the Pd-Catalyzed Alkenylation with Zn, Al, and Zr Organometals.

On the other hand, it has become increasingly clear in recent years that some bidentate ligands, such as DPEphos[54] and dppf,[55] are very frequently superior to simple monodentate phosphines. In less demanding cases, their differences may not be readily noticeable or hardly significant, but in other more demanding cases, these differences become significant. *Procedure II (Modern Standard Conditions)*, employing bidentate ligands, should be considered as needed. Yet other procedures may be considered for solving even more difficult problems.

Even in cases where the differences among two or more procedures seem very minor at high catalyst loadings (1–5 mol %), they usually become more noticeable and significant at lower catalyst loadings. The catalyst loading level or catalyst turnover number (TON) is a potentially very significant issue in the practical application of the Pd-catalyzed cross-coupling. For example, even if a Pd catalyst costs $10,000/mol, it would effectively cost a mere $1–10/mol at a TON level of $10^3$–$10^4$. Since the overall cost of operation also depends on the costs of other reagents, the practical value of attaining extremely high TONs (>$10^6$) may be questioned. Nevertheless, the currently prevalent level of TON $\leq 10^2$ should be elevated to $10^3$–$10^5$ in most cases. Recent studies indicate that the use of some chelating ligands, such as DPEphos and dppf, in conjunction with organometals containing Zn, B, and In, as well as Al–Zn and Zr–Zn combinations, can readily achieve TONs > $10^4$.[61]

## 2.3. Alkenyl–Aryl, Aryl–Alkenyl, and Alkenyl–Alkenyl Coupling Reactions

### 2.3.1. Alkenyl–Aryl and Aryl–Alkenyl Couplings

Both of these reactions produce aryl–substituted alkenes or styrene derivatives. Both protocols involving the Negishi coupling are generally satisfactory, but the following considerations might be important in choosing one over the other: (i) In cases where the required alkenyl reagents are readily accessible via hydrometallation or carbometallation, first consideration should be given to generating the alkenylmetals in situ and carrying out the alkenyl–aryl cross-coupling in the same pot. (ii) On the other hand, many readily available alkenyl electrophiles, such as vinyl bromide, vinylidene chloride and bromide, and (*E*)-3-bromo-2-methylacrylic acid derivatives, favor the aryl–alkenyl coupling protocol. (iii) In some cases, alkenyl electrophiles are most readily accessible from the corresponding carbonyl compounds in the forms of alkenyl triflates or phosphates. In these cases, the aryl–alkenyl coupling protocol would be favored.

Since Al, Zr, and Zn offer a wide range of hydrometallation and carbometallation reactions, and since Zn along with Al–Zn and Zr–Zn combinations are among the most favorable metals in the Pd-catalyzed cross-coupling, both alkenyl–aryl and aryl–alkenyl Negishi cross-coupling reactions rank among the most satisfactory methods for forming the required C–C bonds. Although the number of applications to the synthesis of natural products is still rather limited, the examples reported thus far point to the potential utility and versatility of these reactions (**Scheme 2**).[62–64] A recent application of the Pd-catalyzed reaction of an alkenylzirconium derivative with a bromoxazole to the synthesis of (–)-diazonamide A is especially noteworthy.[64] Other notable examples include the synthesis of alkenyl-substituted nucleosides[65] and a phorboxazole A model.[66]

### 2.3.2. Alkenyl–Alkenyl Coupling

Mainly during the past decade, the Pd-catalyzed alkenyl–alkenyl coupling involving Al and Zr has been extensively applied to the synthesis of conjugated dienes and oligoenes (**Table 1**).[67–88] In many of these reactions, $ZnBr_2$ or $ZnCl_2$ was utilized as a promoter or cocatalyst. In some cases where the Al–Zn or Zr–

Zn combination proved to be less than satisfactory, the use of preformed alkenylzincs derived from the corresponding Li or Mg precursors was demonstrated to be generally superior to them. In some cases, however, a useful synergism was observed between Al or Zr and In, which rendered $InCl_3$ superior to $ZnBr_2$ or $ZnCl_2$ as a cocatalyst.[60] Overall, the Pd-catalyzed alkenyl–alkenyl coupling involving Al, Zr, and Zn represents one of the most generally applicable and satisfactory protocols for the synthesis of conjugated dienes and oligoenes. Nevertheless, it should not be overlooked that several other metals and metalloids including Mg, B, Sn, Si, and Cu have also been employed satisfactorily in many cases.[1,5,6,7,9–13]

## 2.4. Alkynyl–Alkenyl and Alkenyl–Alkynyl Coupling Reactions

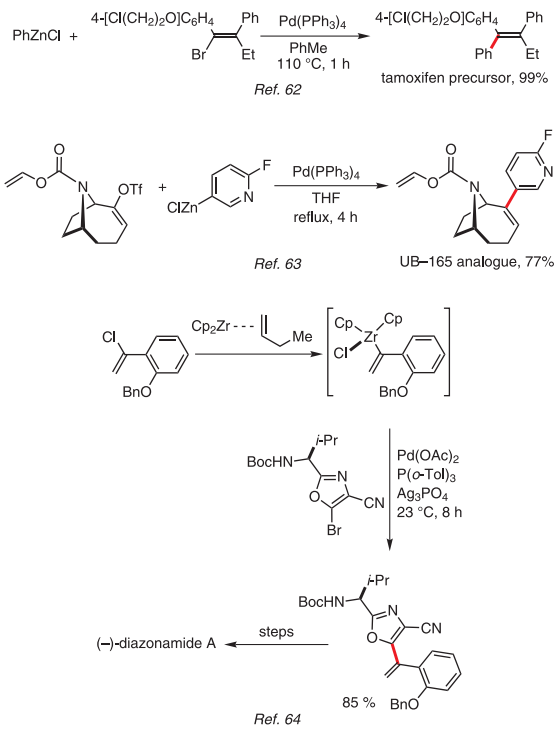
Although the Pd-catalyzed reaction of alkenylmetals containing Al or Zr with 1-iodo-1-hexyne in the presence of $ZnCl_2$ was reported as early as 1978,[23] the alkenyl–alkynyl coupling protocol has not been widely used for the synthesis of conjugated enynes. A notable exception is the synthesis of enediynes by the reaction of (*Z*)-1,2-bis(trimethylstannyl)ethylene with α,ω-diiododiynes.[15] It is generally more convenient to use the alkynyl–alkenyl coupling protocol for the synthesis of conjugated enynes. This reaction utilizes alkynylzincs and provides one of the most satisfactory, generally applicable, and convenient routes to conjugated enynes (**Table 2**).[80,85,87,89–94] In many less demanding cases, the Sonogashira coupling[1a] has probably been most widely used. However, it has recently been shown that its scope is significantly more limited than the alkynylzinc protocol. Thus, for example, it has often been problematic to use alkynes containing electron-withdrawing groups, such as an ester, in the Sonogashira coupling.[15] Direct synthesis of terminal alkynes without protection–deprotection by this reaction has not been practical either. As discussed earlier, it is also possible to use several other classes of alkynylmetals and metalloids containing Mg, B, Al, In, Si, Sn, and others. In cases where alkynylmetals containing Mg are satisfactory, their use should be considered before converting them into other alkynylmetals. Since alkynylmetals containing B, Al, In, Si, and Sn are prepared mainly from alkynylmetals containing Mg, Li, or some other alkali metal, and since they are generally less reactive than alkynylzincs, their use in place of Mg or Zn should be well justified.[1a,15,95]

## 2.5. Benzylation, Allylation, and Propargylation of Alkenylmetals and Alkenyl Electrophiles

In this section, six types of cross-coupling reactions are discussed. These lead to three types of products: allylarenes (or benzylalkenes), 1,4-dienes, and 1,4-enynes. Relevant findings reported prior to 1998 have been comprehensively reviewed.[1a]

### 2.5.1. Alkenyl–Benzyl and Benzyl–Alkenyl Coupling Reactions for the Synthesis of Allylarenes

Benzylation by the Pd-catalyzed cross-coupling is a generally favorable process that can be achieved satisfactorily via either alkenyl–benzyl or benzyl–alkenyl coupling. If alkenylmetals are more readily accessible than the corresponding halides, the alkenyl–benzyl coupling may be considered first. If, on the other hand, alkenyl electrophiles are more readily available than the corresponding alkenylmetals, the benzyl–alkenyl coupling should be considered first. It is also important to note that benzylzincs can usually be more cleanly and readily prepared than the corresponding Li- or Mg-containing benzylmetals by direct metallation of benzyl bromides or chlorides with Zn metal with minimum complications arising from homocoupling and other




**Scheme 2**. Synthesis of Natural Products and Related Compounds via the Negishi Alkenyl–Aryl or Aryl–Alkenyl Coupling.

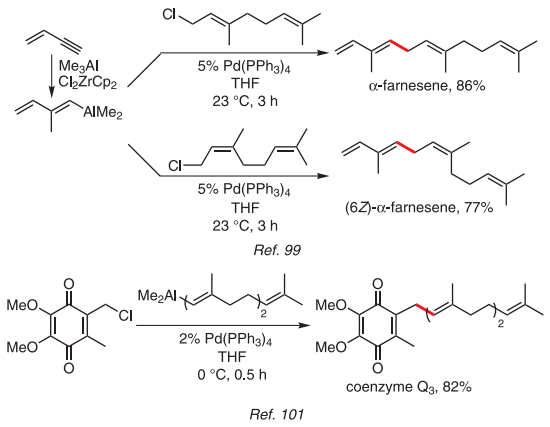
**Table 1. The Pd-Catalyzed Alkenyl–Alkenyl Coupling with Al, Zr, and Zn Organometals in Natural Product Synthesis**

| Year | Natural Product or Related Compound | Major Author | Ref. |
|---|---|---|---|
| 1987 | Piperovatine | Crombie, L. | 67 |
| 1991 | Methyl dimorphecolate | Duffault, J. M. | 68 |
| 1991 | Vitamin A | Negishi, E. | 69 |
| 1995 | Papulacandin D | Barrett, A. G. M. | 70 |
| 1996 | Discodermolides | Schreiber, S. L. | 71 |
| 1996 | Zaragozic acid C | Paterson, I. | 72 |
| 1996 | Nakienone B | Negishi, E. | 73a |
| 1997 | Nakienone A | Negishi, E. | 73b |
| 1997 | Gadain and Savinin | Rossi, R. | 74 |
| 1998 | Okinonellin B | Romo, D. | 75 |
| 1998 | (±)-Carbacyclin | Negishi, E. | 76 |
| 1999 | Lissoclinolide | Negishi, E. | 77 |
| 1999 | Reveromycin B | Theodorakis, E. A. | 78 |
| 2000 | Pitiamide A | Wipf, P. | 79 |
| 2000 | Xerulin | Negishi, E. | 80 |
| 2001 | β- and γ-Carotenes | Negishi, E. | 81 |
| 2001 | Eunicenone A | Corey, E. J. | 82 |
| 2001 | FR901464 (antitumor antibiotic) | Jacobsen, E. N. | 83 |
| 2002 | Motuporin | Panek, J. S. | 84 |
| 2004 | *cis*- and *trans*-Bupleurynol | Organ, M. G. | 85 |
| 2004 | (–)-Callystatin A | Panek, J. S. | 86 |
| 2004 | 6,7-Dehydrostipiamide | Negishi, E. | 87 |
| 2004 | Xerulinic acid | Brückner, R. | 88 |

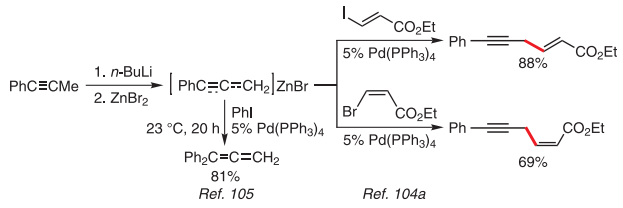
**Table 2. The Pd-Catalyzed Coupling between Alkynylmetals Containing Zn or Mg and Alkenyl Electrophiles in Natural Product Synthesis**

| Year | Natural Product or Related Compound | Major Author | Ref. |
|---|---|---|---|
| 1982 | Octa-2,3-dien-5,7-diyn-1-ol[a] | Vermeer, P. | 89 |
| 1988 | Marasin | Boersma, J. | 90 |
| 1997 | Freelingyne | Negishi, E. | 91 |
| 2000 | Xerulin | Negishi, E. | 80 |
| 2000 | (±)-Harveynone | Negishi, E. | 92 |
| 2000 | (±)-Tricholomenyn A | Negishi, E. | 92 |
| 2001 | (–)-Salicylihalamides A and B | Fürstner, A. | 93 |
| 2004 | Ant venom | Organ, M. G. | 94 |
| 2004 | *cis*- and *trans*-Bupleurynol | Organ, M. G. | 85 |
| 2004 | 6,7-Dehydrostipiamide | Negishi, E. | 87 |

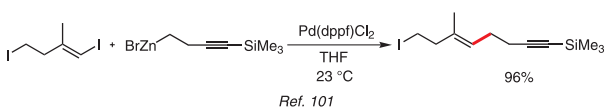
[a] A metabolite of *Cortinellus berkeleyanus*.




**Scheme 3**. The Pd-Catalyzed Alkenyl–Allyl Coupling in the Synthesis of Natural Products.




**Scheme 4**. The Pd-Catalyzed Coupling of Allenylzinc Derivatives.




**eq 2**

side reactions.[20] This usually makes Zn the metal of choice in the Pd-catalyzed benzyl–alkenyl coupling.

### 2.5.2. Allyl–Alkenyl and Alkenyl–Allyl Coupling Reactions for the Synthesis of 1,4-Pentadienes

Despite the fact that the reaction of allyl(tributyl)stannane with bromobenzene in the presence of $Pd(PPh_3)_4$, reported in 1977, is probably the first example of Pd-catalyzed allylation of organic halides,[96] the allyl–alkenyl coupling is generally to be avoided in favor of the alkenyl–allyl coupling for a couple of reasons. Firstly, allylmetals are generally prepared from the corresponding allyl halides. Their preparation with retention of regio- and stereochemistry is frequently quite challenging, generally more challenging than the preparation of the corresponding electrophiles. Secondly, allylmetals with a carbon–carbon double bond in the β,γ position tend to act as catalyst poisons more readily than benzylmetals. In this regard, allylmetals of low intrinsic nucleophilicity containing Sn and Si may be promising in the absence of other difficulties. This point largely remains to be experimentally established, however.

On the other hand, the Pd-catalyzed alkenyl–allyl coupling reactions of Zn, Al, and Zr alkenylmetals are generally favorable processes, even though unwanted allyl rearrangement accompanied by stereoisomerization can be a usually minor but potentially serious side reaction in cases where allyl groups are γ-mono- or β,γ-disubstituted. Allylic electrophiles are often so reactive toward Pd that allylic chlorides as well as a wide variety of oxygenated allyl derivatives, such as acetates, carbonates, phosphates, and even silyl ethers, are sufficiently reactive in this reaction. γ,γ-Disubstituted allyl derivatives can often be used with little or no sign of regio- and stereoisomerization. In marked contrast with the Tsuji–Trost allylation,[97] the Pd-catalyzed alkenyl–allyl coupling reactions proceed with clean stereoinversion at the allylic carbon center.[98]

The number of natural products synthesized by the Pd-catalyzed alkenyl–allyl coupling is still relatively small. Nonetheless, strictly regio- and stereospecific syntheses of α-farnesene and its 6*Z* isomer,[99] (+)-hennoxazole A,[100] as well as a series of coenzyme Q's and menaquinones,[101] persuasively point to its synthetic potential (**Scheme 3**). Both Pd and Ni complexes are highly satisfactory for catalyzing the alkenyl–benzyl and alkenyl–allyl coupling reactions.[99,101–103]

### 2.5.3. Pd-Catalyzed Allenylation and Propargylation

The Pd-catalyzed reactions of various types of organometals containing aryl, alkenyl, alkynyl, allenyl, and alkyl groups with either progargyl or allenyl electrophiles give predominantly or exclusively the corresponding allenes rather than alkynes.[1a] Generally, zinc appears to be the most satisfactory countercation among several others including Mg, Cu, Ag, B, Al, and Sn.[1a]

The Pd-catalyzed reaction of propargylmetals or allenylmetals is less predictable than the corresponding reaction of propargyl or allenyl electrophiles. Both 1,4-enynes and enallenes or arylallenes have been obtained, depending on the reactant structures and reaction conditions (**Scheme 4**).[104,105]

## *2.6. Alkyl–Alkenyl and Alkenyl–Alkyl Coupling Reactions*

Alkyl halides and related electrophiles are substantially less reactive toward Pd than unsaturated organic electrophiles including those containing aryl, alkenyl, alkynyl, acyl as well as allyl, benzyl, and propargyl groups. The lower reactivity of alkyl halides toward Pd has been explained in terms of the lack of a proximal π bond. A difference in reactivity of at least a 100-fold between alkenyl

and alkyl iodides has been observed (**eq 2**).[101] Mainly for this reason, Pd-catalyzed alkylation of alkenyl derivatives has been achieved mostly via the alkyl–alkenyl coupling. However, alkyl halides are not inert towards Pd. For example, the use of highly nucleophilic Pd complexes containing bulky trialkylphosphines, such as $PCyp_3$(Cyp = cyclopentyl) and $PCy_3$ (Cy = cyclohexyl), has permitted the alkenyl–alkyl coupling between alkenylzinc derivatives and alkyl iodides, bromides, and tosylates.[56] Also noteworthy is the reaction of alkenylzirconium derivatives with alkyl bromides in the presence of 2.5 mol % of $Pd(acac)_2$ and LiBr (2 equiv) in THF–NMP.[106]

Despite recent promising developments such as those mentioned above, the Pd-catalyzed alkylation of alkenyl derivatives is still achieved mostly by the alkyl–alkenyl coupling protocol. In this regard, alkylzincs are generally superior to the other alkylmetals that have been examined to date, although alkylborons[107] and alkylmagnesiums[108] are satisfactory in many cases. In some reactions with alkenyl chlorides, Mg is even distinctly superior to Zn (**eq 3**).[29] Another noteworthy recent development is that alkylalanes generated in situ via Zr-catalyzed asymmetric carboalumination of alkenes can now be vinylated with vinyl bromide under the Zn–Pd double metal-catalyzed conditions in ca. 70% overall yields in one pot.[109] This reaction will be further discussed in Section 3.1. A similar hydrozirconation–cross-coupling tandem process is also promising.[110]

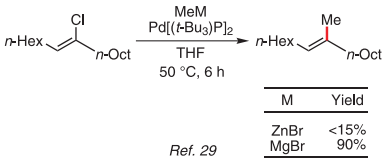
One should bear in mind that, in the Pd-catalyzed alkylation with alkylzincs or perhaps organozincs in general, the precise composition of alkylzincs, which significantly depends on the methods of their generation, affects the course of the subsequent cross-coupling process. One important determining factor is the alkyl/Zn/Li (or Mg) ratio. In a synthesis of (–)-discodermolide, it was shown to be desirable to add 3 equiv of *t*-BuLi to an alkyl iodide premixed with $ZnCl_2$ (**Scheme 5**).[111]

One potentially attractive recent development is a Pd-catalyzed asymmetric hydroboration–transmetallation (B→Zn)–alkenylation process producing chiral alkenes of 52–83% ee's.[112] If both the enantiomeric purity and the modest yields of 35–41% can be improved, it would prove to be a useful asymmetric synthetic tool. Presumably, the chiral borane intermediates are not sufficiently reactive in the desired Pd-catalyzed alkenylation, although no mention was made to this effect in the paper. The corresponding Pd-catalyzed acylation led to similar yields and stereoselectivities. These results, taken together with a previously developed Pd- or Ni-catalyzed vinylation of chiral benzylic secondary alkylmetals containing Mg or Zn,[1a] suggest that the development of a highly satisfactory and widely applicable Pd- or Ni-catalyzed asymmetric alkyl–alkenyl coupling might be imminent. A large number of natural products and related compounds have been synthesized by using the Pd-catalyzed alkenylation of alkylzinc derivatives (**Table 3**).[49,86,101,109,111,113–135]

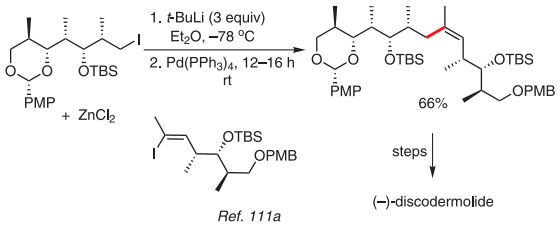
## 2.7. Acylation and Cyanation of Alkenyl Derivatives

### 2.7.1. Acylation of Alkenylmetals

The Pd-catalyzed reaction of a wide variety of organozincs with acyl chlorides[136] is one of the most generally applicable methods of acylation of organometals for the synthesis of ketones. Organozincs containing alkyl, aryl, alkenyl, and alkynyl groups have been successfully used. Particularly noteworthy are those cases where alkenyl- and alkynylzincs are utilized. α,β-Unsaturated ketones obtained as the products can, in principle, undergo competitive conjugate addition, as has been observed with organocoppers. However, this has not been a serious side reaction in the Pd-catalyzed acylation of alkenylzincs (**eq 4**).[136]




**eq 3**




**Scheme 5**. The Pd-Catalyzed Alkyl–Alkenyl Coupling with an Alkylzinc in a Total Synthesis of (–)-Discodermolide.

**Table 3. Alkenylation of Alkylzinc Derivatives in the Synthesis of Natural Products and Related Compounds**

| Year | Natural Product | Major Author | Ref. |
|---|---|---|---|
| 1980 | Dendrolasin | Negishi, E. | 113 |
| 1980 | Mokupalide | Negishi, E. | 113 |
| 1980 | (2*E*,6*E*)-Farnesol | Negishi, E. | 114 |
| 1987 | (+)-Casbene | McMurry, J. E. | 115 |
| 1989 | (±)-Ageline A | Tokoroyama, T. | 116 |
| 1989 | Yellow scale pheromone | Millar, J. G. | 117 |
| 1995 | (–)-Discodermolide | Smith, A. B., III | 111 |
| 1998 | (+)-Amphidinolide J | Williams, D. R. | 118 |
| 1999 | Brevetoxin A | Nicolaou, K. C. | 119 |
| 1999 | (–)-Epothilone B | Schinzer, D. | 120 |
| 1999 | (+)-Pumiliotoxins A and B | Kibayashi, C. | 121 |
| 2001 | (*E*)- and (*Z*)-γ-Bisabolenes | Negishi, E. | 49 |
| 2001 | (–)-4a,5-Dihydrostreptazolin | Cossy, J. | 122 |
| 2001 | Mycolactones A and B | Kishi, Y. | 123 |
| 2002 | Coenzymes $Q_3$ and $Q_{10}$ | Negishi, E. | 101 |
| 2002 | *trans*-Epothilone A | Altmann, K. H. | 124 |
| 2002 | (2*E*,6*Z*), (2*Z*,6*Z*), and (2*Z*,6*E*)-Farnesols | Negishi, E. | 101 |
| 2002 | (2*E*,6*Z*,10*E*)-Geranylgeraniol | Negishi, E. | 101 |
| 2002 | Menaquinone-3 | Negishi, E. | 101 |
| 2002 | Oleandolide | Panek, J. S. | 125 |
| 2002 | Sphingofungin F | Ham, W.-H. | 126 |
| 2002 | Ionomycin | Lautens, M. | 127 |
| 2003 | Borrelidin | Morken, J. P. | 128 |
| 2003 | Delactonmycin | Pilli, R. A. | 129 |
| 2004 | (–)-Callystatin A | Panek, J. S. | 86 |
| 2004 | Capensifuranone | Williams, D. R. | 130 |
| 2004 | (+)-Murisolin | Curran, D. P. | 131 |
| 2004 | Scyphostatin side chain | Negishi, E. | 132 |
| 2004 | Scyphostatin | Katoh, T. | 133 |
| 2004 | Siphonarienal | Negishi, E. | 134 |
| 2004 | Siphonarienolone | Negishi, E. | 134 |
| 2004 | Siphonarienone | Negishi, E. | 134 |
| 2005 | Ionomycin (a key intermediate of) | Negishi, E. | 109 |
| 2005 | Borrelidin (a key intermediate of) | Negishi, E. | 109 |
| 2005 | Preen gland wax of graylag goose *Anser anser* | Negishi, E. | 135 |

Although the Pd-catalyzed acylation of organozincs has been applied to the synthesis of several natural products, none involves a Pd-catalyzed alkenylation. A few interesting variants of the Pd-catalyzed acylation of organozincs have also been developed. In one of them, thiol esters are employed in place of acyl chlorides.[137] This reaction has been applied to the synthesis of at least one α,β-unsaturated enone, 1-(4-methoxyphenyl)-4-nonen-3-one, in 79% yield.[137b] However, it is not readily apparent what advantage this reaction offers over the corresponding reaction with the acid chloride, from which the required thiol ester is prepared.

A few other more recent variations on the Pd-catalyzed acylation of organozincs include the Pd- or Ni-catalyzed reactions of organozincs with carboxylic anhydrides[138,139a–c] and acyl fluorides.[139d] In one procedure, carboxylic anhydrides are generated in situ from alkali metal carboxylates and $ClCO_2Et$.[138] Desymmetrization of symmetrical anhydrides under the influence of a chiral ligand appears to be promising. However, no examples are known in which alkenylzincs were used.

### 2.7.2. Cyanation of Alkenyl Electrophiles

The cyanation of alkyl halides with alkali metal cyanides and that of aryl halides with a stoichiometric amount of CuCN, i.e., the Rosenmund–Von Braun reaction, represent classic C–C bond-forming reactions. Their transition-metal-catalyzed counterpart was first reported by Takagi.[140a] Under modified conditions, the reaction has also been applied to the cyanation of alkenyl electrophiles.[141,142] Over the past decade or so, the use of other metal countercations and other reaction parameters has made the Pd-catalyzed cyanation more widely applicable. In particular, aryl bromides and even chlorides can now be satisfactorily cyanated with $Zn(CN)_2$ in DMF or DMA in the presence of Pd catalysts containing $PPh_3$, dppf, or other phosphines (**eq 5**).[1a,143,144] However, despite extensive recent developmental work, little, if any, has been published on the cyanation of alkenyl electrophiles with $Zn(CN)_2$.

## *2.8. α Alkenylation of Metal Enolates and α-Halo-α,β-unsaturated Carbonyl Compounds*

The alkenylation, arylation, and alkynylation of α-halo- and β-halo-α,β-unsaturated carbonyl compounds are highly desirable synthetic operations.[145] The coupling with β-halo-α,β-unsaturated carbonyl compounds is a fundamentally very favorable process and has been termed *conjugate substitution*. Its Pd-catalyzed version, reported first in 1976,[17] has since been extensively developed and applied to the synthesis of natural products and other organic compounds.[1a] On the other hand, the corresponding reaction of α-halo-α,β-unsaturated carbonyl compounds has proved to be much more demanding.[145b] Since the classical method of α substitution of carbonyl compounds by C–C-bond-forming reactions of enolates had until recently been practically limited to α substitution with alkyl groups, it was very desirable to overcome this critical limitation. Fortunately, all three classes of unsaturated carbon atom (alkenes, alkynes, and arenes) can be accommodated, in principle, by various protocols of Pd- or Ni-catalyzed α substitution of carbonyl compounds. One of the two most widely investigated protocols is the direct α substitution of metal enolates catalyzed by Pd or Ni complexes (Pd- or Ni-catalyzed *direct α substitution* of metal enolates).[1a] This is clearly one of the most straightforward, efficient, and desirable approaches. In many demanding and delicate cases, however, this approach frequently suffers from difficulties associated with several aspects of the reaction most notably regioselectivity. To cope with difficulties pertaining to regiochemical control, an alternate approach involving Pd- or Ni-catalyzed α substitution of α,β-unsaturated carbonyl compounds and related derivatives (Pd- or Ni-catalyzed *indirect α substitution* via α substitution of α-halo-α,β-unsaturated carbonyl compounds) has been developed.[1a,145b] The relationship between these two methods is shown in **Scheme 6**.[146] Since α,β-unsaturated carbonyl compounds often serve as precursors to regiodefined enolates, their use as the starting carbonyl compounds in the latter approach is readily justified. Their α halogenaton amounts to an additional step in comparison with the direct α substitution of regiodefined enolates derived from α,β-unsaturated enones. In many cases, however, the need for this extra step may be more than justified by (i) being able to strictly control the regiochemistry of the α substitution, and (ii) generally more favorable C–C-bond formation through the use of α-halo-α,β-unsaturated carbonyl compounds than by direct α substitution of enolates. Furthermore, in cases where α-substituted α,β-unsaturated carbonyl compounds are the desired final products, the latter protocol with α-halo-α,β-unsaturated carbonyl compounds should prove to be more advantageous than the α substitution of enolates. Although different, a related Pd-catalyzed α alkenylation of α-hetero-substituted β,γ-unsaturated carbonyl compounds is also noteworthy (**Scheme 7**).[147]

Both types of α substitution reactions reported before 2000 have been systematically and comprehensively discussed.[1a] Some of the more recent examples of the application to natural product synthesis[74,92,148,149] of the Pd-catalyzed α substitution of α-halo-α,β-unsaturated carbonyl compounds with alkenyl- and alkynylzincs, are shown in **Scheme 8**.

## 3. Special Topics of the Pd-Catalyzed Alkenylation

## *3.1. Pd-Catalyzed Hydrometallation–Cross-Coupling and Carbometallation–Cross-Coupling Tandem Reactions*

The hydrometallation–cross-coupling and carbometallation–cross-coupling tandem reactions, with or without the use of $ZnBr_2$ or $ZnCl_2$ as a cocatalyst,[16,17,21–24] have played a major role in the Pd-catalyzed alkenylation involving Zn, Al, and Zr as well as B, Sn, and Cu. These "one-pot" procedures not only are step-economical, but also permit minimization of the use of cost-adding iodination or bromination and subsequent lithiation or other metallation reactions. In pursuit of highly satisfactory syntheses of alkenes via the Pd-catalyzed alkenylation, iterative procedures involving a minimum number of steps in each cycle, preferably one, have been recognized as being highly desirable in the syntheses of terpenoids, carotenoids, polypropionates, and other natural products containing oligomeric structural units. In this section, some of the noteworthy advances in this area, achieved mainly over the past decade, are presented with a focus on their applications to the synthesis of natural products.

### 3.1.1. Hydrozirconation–Cross-Coupling Tandem Reactions of 2-Alkynes

Whereas terminal alkynes can be hydrometallated highly regioselectively (typically >98%) with metal hydrides containing B, Al, and Zr, the corresponding reactions of internal alkynes are generally less regioselective.[150,151] However, the hydrozirconation with $HZrCp_2Cl$, which contains not only bulky ligands but also a transition metal, can be more readily equilibrated under thermal conditions in the presence of an excess of $HZrCp_2Cl$ than the corresponding reactions with boron and aluminum hydrides. Thus, the regioselectivity observed with 2-alkynes containing secondary alkyl groups can be improved to nearly 100% (**Scheme 9**).[84,151,152] This procedure has been applied to the synthesis of some natural products, such as reveromycin B[78] and motuporin[84] (**Scheme 10**).

### 3.1.2. Iterative Tandem Carboalumination–Vinylation for the Asymmetric Synthesis of Reduced Polypropionates

The Zr-catalyzed asymmetric carboalumination reaction (ZACA reaction) of terminal alkenes[48,152] can be followed by (i) oxidation with $O_2$; (ii) iodination with $I_2$, $PPh_3$, and imidazole; and (iii) lithiation with *t*-BuLi, zincation with $ZnBr_2$ or $ZnCl_2$, and Pd-catalyzed vinylation to produce another terminal alkene, which can be subjected to another round of this three-step cycle.[153] This catalytic three-step process has been successfully applied to efficient, catalytic, and asymmetric syntheses of reduced polypropionates and related compounds, such as siphonarienal,[128] siphonarienone,[128] siphonarienolone,[128] and the scyphostatin side chain.[127]

The long-pending problem of how to carry out alkene hydroalumination, to generate alkylalanes, and directly achieve their Pd- or Ni-catalyzed cross-coupling has recently been overcome in the case of vinylation.[109] This development has permitted iteration of the one-pot procedure for the unprecedentedly efficient and asymmetric construction of the reduced polypropionate segments of ionomycin and borrelidin (**Scheme 11**).[109]

### 3.1.3. Iterative Carboalumination–Pd-Catalyzed Alkylation for the Synthesis of Terpenoids Containing 1,5-Diene Units

Although no one-pot carbometallation–cross-coupling tandem process is involved, an iterative two-step homologation procedure for the synthesis of terpenoids containing 1,5-diene units, such as mokupalide was developed as early as 1980.[113]

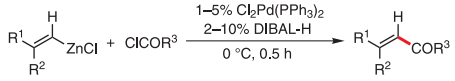
In many cases where there are three or more isoprene units in the target molecule, it would be more efficient to devise iterative procedures involving one-step incorporation of one isoprene unit.[47] This has been successfully applied to the synthesis of coenzymes $Q_n$ (n = 3,10), menaquinone 3, the less commonly encountered (2*E*,6*Z*)- and (2*Z*,6*Z*)-farnesols, and even (2*E*,6*Z*,10*E*)-geranylgeraniol (**Scheme 12**).[101] The formation of undesired stereoisomers was not detected in all of these syntheses, although successful synthetic designs must carefully avoid the potentially competitive formation of byproducts, such as cyclopropylcarbinyl derivatives, and pay extra care to the use of the potentially more capricious (*Z*)-1,4-diiodo-2-methyl-1-butene.[109]

## *3.2. Pd-Catalyzed Double Alkenylation Using 1,1-Dihalo-1-alkenes and Related Compounds*

As discussed throughout Sections 2 and 3.1, the regio- and stereoselective hydrometallation of internal alkynes and carbometallation of terminal alkynes provide convenient and selective routes to trisubstituted alkenes. Even so, there are many instances of trisubstituted alkenes, where new and alternate synthetic routes are desirable. Three related classes of 1,1-disubstituted 1-alkenes (**Figure 3**) have collectively provided some useful routes to trisubstituted alkenes. The discussion in this section will focus mainly on the selective and stepwise Pd-catalyzed double cross-coupling of 1,1-dihalo-1-alkenes and their use in natural product synthesis.

### 3.2.1. Pd-Catalyzed Double Cross-Coupling Reactions of 1,1-Dihalo-1-alkenes with Zn, Al, and Zr Organometals

The palladium-catalyzed trans-selective monoarylation of 1,1-dichloro-1-alkenes with arylmagnesium derivatives was first reported in 1987.[154] Several examples of a second Pd-catalyzed arylation, also with arylmagnesium derivatives, were presented




| $R^1$ | $R^2$ | $R^3$ | Yield | Stereoselectivity |
|---|---|---|---|---|
| *n*-Pent | H | Me | 76% | >99% *E* |
| *n*-Hex | H | MeO | 56% | >98% *E* |
| *n*-Hex | Me | Me | 77% | >98% *E* |

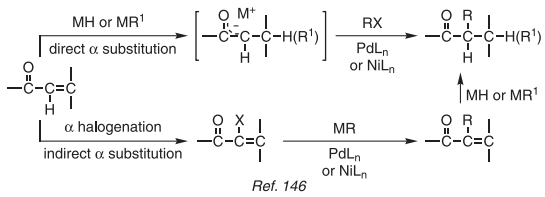
*Ref. 136*

**eq 4**


Ar = aryl; X = I, Br, Cl
$PdL_n$ = $Pd(PPh_3)_4$, $Pd(dppf)Cl_2$, others

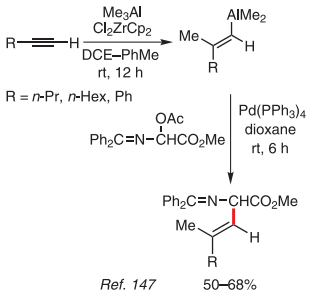
*Ref. 143,144*

**eq 5**



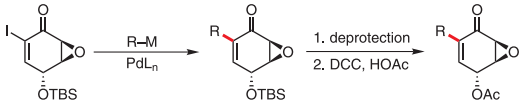

*Ref. 146*

**Scheme 6**. Pd- or Ni-Catalyzed Direct α Substitution vs. Indirect α Substitution.




*Ref. 147* 50–68%

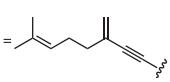
**Scheme 7**. Pd-Catalyzed α Alkenylation of α-Imino-α-acetoxyacetates.



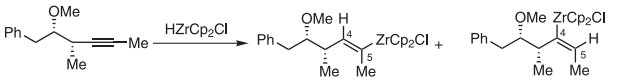

| M | $PdL_n$ | Cond. | Yield[a] | Ref. |
|---|---|---|---|---|
| ZnBr | $Pd(dba)_2$,TFP | DMF, 25 °C, 1 h | 80% | 92 |
| $SnBu_3$ | $Cl_2Pd(PPh_3)_2$ | CuI, NMP | 39% | 148b |
| H | $Cl_2Pd(PPh_3)_2$ | CuI, $(i\text{-Pr})_2NH$ | 54% | 149 |

[a] Yield of the cross-coupling step.

(±)-tricholomenyn A



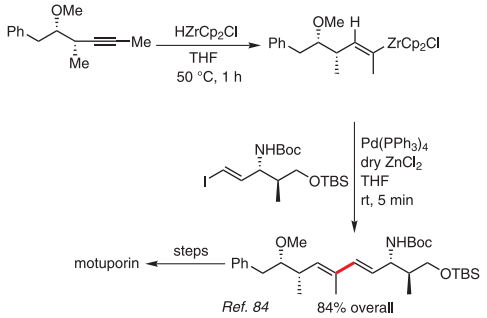

**Scheme 8**. Pd-Catalyzed α Alkenylation and α Alkynylation of α-Iodo-α,β-unsaturated Carbonyl Compounds in Natural Product Synthesis.



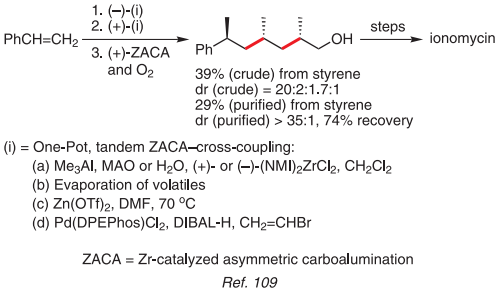

| Equiv. of $HZrCp_2Cl$ | Solvent | Temp. | Time | C(Zr)-5/C(Zr)-4 |
|---|---|---|---|---|
| 1.5 | PhH | 45 °C | 0.3 h | 75:25 |
| 2.0 | PhH | 50 °C | 4 h | 100:0 |
| 2.0 | THF | 50 °C | 1 h | 100:0 |

*Ref. 84c*

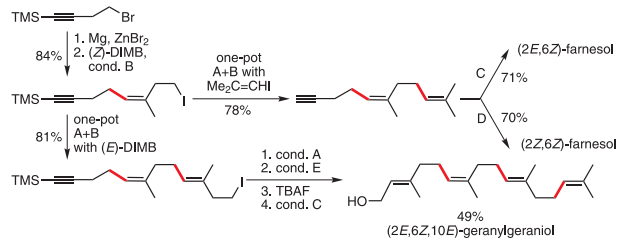
**Scheme 9**. Improvement of the Regioselectivity of the Hydrozirconation of 2-Alkynes.




**Scheme 10**. The Synthesis of Natural Products by the Hydrozirconation of 2-Alkynes Followed by Cross-Coupling.




**Scheme 11**. Iterative One-Pot Homologation of Reduced Polypropionates via ZACA–Pd-Catalyzed Vinylation.




**Scheme 12**. Iterative One-Pot Homologation of Terpenoids Containing 1,5-Diene Units with (*E*)- and (*Z*)-1,4-Diiodo-2-methyl-1-butenes.

in the same paper. In the only example of trans-selective monoalkylation reported in the same paper, the use of *n*-BuMgBr did not give the desired product at all, but that of *n*-BuZnCl led to the desired monobutylated product, *trans*-2-chloro-1-phenyl-1-hexene, in 81% yield. The Pd-catalyzed second alkylation of this monobutylated intermediate with *n*-HexMgBr gave the desired trisubstituted alkene with full retention of configuration in 77% yield. Evidently, the first-stage alkylation was strongly aided by the fact that the starting compound was β,β-dichlorostyrene, since attempts to achieve a related trans-selective monoalkylation of 2-alkyl-substituted 1,1-dichloro- or 1,1-dibromo-1-alkenes under the same conditions failed.[154]

Many subsequently published papers reported Pd-catalyzed trans-selective monosubstitution reactions of 1,1-dichloro- and 1,1-dibromo-1-alkenes with arylzincs,[155] alkenylzincs,[77,156a] alkenylzirconiums,[77] alkenylborons,[157] aryl- and vinylstannanes,[158] and alkynes in the presence of CuI and a base.[156b,159] However, the scope of the second substitution via Pd-catalyzed cross-coupling to produce trisubstituted alkenes had until recently been essentially limited to a few examples. In particular, there was only one example of methylation in the second step of the disubstitution of an apparently highly activated β,β-dibromostyrene derivative.[158]

With the goal of developing Pd-catalyzed, stepwise double substitution procedures that are well-suited for the synthesis of various types of natural product, a series of systematic investigations have been conducted, which focused on the Pd-catalyzed trans-selective single-stage arylation, alkenylation, or alkynylation of 2-alkyl-substituted 1,1-dihalo-1-alkenes—followed by a second-stage alkylation, especially methylation and ethylation (**Scheme 13**).[160–162] These investigations led to the following noteworthy findings:

- Both 1,1-dichloro- and 1,1-dibromo-1-alkenes, readily obtainable from the corresponding aldehydes, can be selectively monosubstituted (≥98% trans) in good yields with aryl-, alkenyl-, and alkynylzinc reagents by using $Pd(DPEphos)Cl_2$ as catalyst. Alkynylzincs are generally superior to terminal alkynes used in conjunction with a catalytic amount of CuI and $(i\text{-}Pr)_2NH$, especially in cases where 1,1-dichloro-1-alkenes are employed.
- In the second-step substitution, alkylation with alkylmetals, such as $Me_2Zn$, $Et_2Zn$, and higher homologues, can be achieved in excellent yields by using $Pd[(t\text{-}Bu)_3P]_2$ as catalyst. Under these conditions, little or no alkene stereoisomerization is observed.
- Perhaps, the most striking finding in this series of investigations is that the second-stage alkylation in the presence of $Pd(DPEphos)Cl_2$ or those Pd complexes containing more conventional phosphines, such as dppf, $PPh_3$, or TFP, is often accompanied by nearly complete stereoinversion of the initially dihalo-bearing double bond.[163] With DPEphos and dppf, ≥97% stereoinversion has been observed in many cases.

1,1-Dihalo-1-alkenes containing a 2-alkenyl or 2-alkynyl group do not undergo stereoinversion at all, whereas the presence of an aryl group in the same position induces partial stereoisomerization. Chelation of Pd by a π bond in the γ,δ position must inhibit stereoinversion. Although the mechanism of this interesting stereoinversion is still unclear at this time, stereoinversion via a π–σ–π rearrangement—widely accepted as the mechanism for stereoinversion of allylmetals—must not be operative, as this mechanism must invariably proceed with double inversions, which were not observed. The mechanism shown in **Scheme 14**, on the other hand, appears to be not only compatible with the observed facts, but also very plausible.

Irrespective of mechanistic details, the synthesis of either *E*,*E* or *Z*,*E* conjugated dienes from the same starting compounds in a high-yielding and stereoselective manner should be of considerable synthetic utility, as suggested by a recent synthesis of (–)-callystatin A.[86]

### 3.2.2. Synthesis of Unsymmetrically Substituted Conjugated Diynes via Pd-Catalyzed Alkenylation with 1,1-Dichloroethylene

Unsymmetrically substituted conjugated diynes have been prepared most commonly by the Cu-catalyzed alkynyl–alkynyl coupling called the Cadiot–Chodkiewicz reaction.[164] This synthesis requires two steps from the two terminal alkynes to be coupled, including the conversion of one or the other alkyne into the corresponding 1-haloalkyne. The main limitation of this method is that the reaction tends to produce rather frequently a mixture of the desired diyne and two unwanted symmetrically substituted diynes.[164] This difficulty has also been observed in the corresponding Pd-catalyzed alkynyl–alkynyl coupling, although some very favorable cases are known. A strictly "cross-selective" route to conjugated diynes via a Pd-catalyzed monoalkynylation of 1,2-dihaloethylenes[165,166] has been devised as a superior alternative, as discussed in Section 3.3. Although highly selective and widely applicable, this reaction suffered from the high cost of the 1,2-dihaloethylenes starting materials. To overcome this drawback, an alternative method that starts with 1,1-dichloroethylenes was developed. It has long been known that the Pd-catalyzed monoalkynylation of inexpensive vinylidene chloride gives 2-chloro-1-en-3-ynes in excellent yields provided that 5 equiv of vinylidene chloride is used.[167] This reaction has been applied in a highly satisfactory and economical synthesis of unsymmetrically substituted conjugated diynes (**Scheme 15**).[168]

### 3.2.3. 1,1-Dimetallo-1-alkenes and 1-Hetero-substituted 1-Alkenylmetals in the Pd-Catalyzed Alkenylation

The hydrometallation and carbometallation of 1-metallo-1-alkynes are often highly regio- and stereoselective, producing 1,1-dimetallo-1-alkenes mostly via syn addition. In cases where the two metals in 1,1-dimetallo-1-alkenes are sufficiently different, monohalogenation and monosubstitution with other heteroatoms can give 1-heterosubstituted 1-alkenylmetals. These 1,1-disubstituted alkenes can, in principle, be converted into various trisubstituted alkenes via a Pd- or Ni-catalyzed cross-coupling. Even though reactions of this class of compounds have been used in the synthesis of temarotene (**Scheme 16**)[169] and discodermolide,[170] the current scope of highly satisfactory and synthetically useful applications appears to be still rather limited. This, however, is potentially a promising field for exploration and development.

## *3.3. Pd-Catalyzed Alkenylation Utilizing 1,2-Dihalo-1-alkenes and Related Compounds*

1,2-Dihaloethylenes are, in principle, a group of attractive synthetic modules or synthons. Even if one considers only Cl, Br, and I, there are six each of (*E*)- and (*Z*)-1,2-dihaloethylenes. Of these, (*E*)-ClCH=CHCl, (*Z*)-ClCH=CHCl, (*E*)-BrCH=CHBr, and (*E*)-BrCH=CHI are commercially available. (*E*)-ClCH=CHI, which is already synthetically useful, might be commercialized in the near future. On the other hand, the synthetic value of ICH=CHI and BrCH=CHCl is not clear at this point. Some of the earlier contributions, mostly by the Linstrumelle–Alami group[171] and that of Rossi,[172] have been reviewed.[1a] In these studies, (*E*)- or (*Z*)-ClCH=CHCl and *E*/*Z* mixtures of BrCH=CHBr were used. An

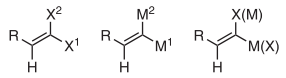
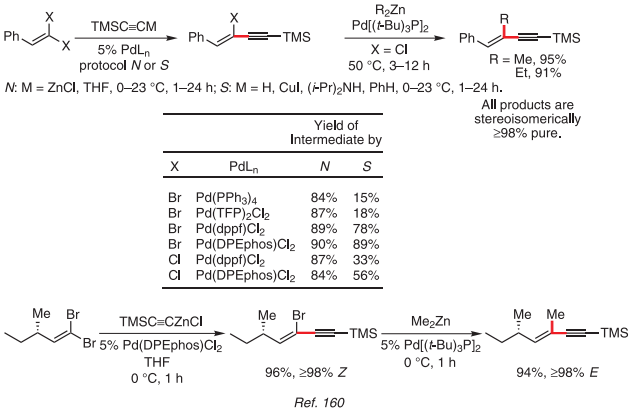
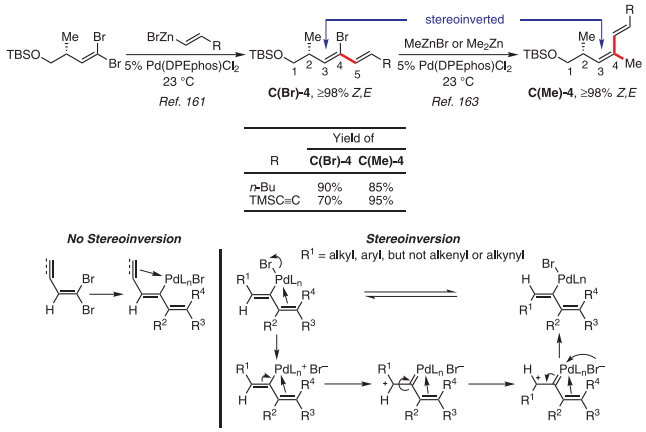


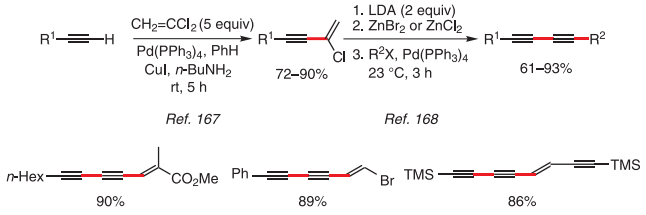
**Figure 3**. 1,1-Dihalo-1-alkenes and Related Compounds.



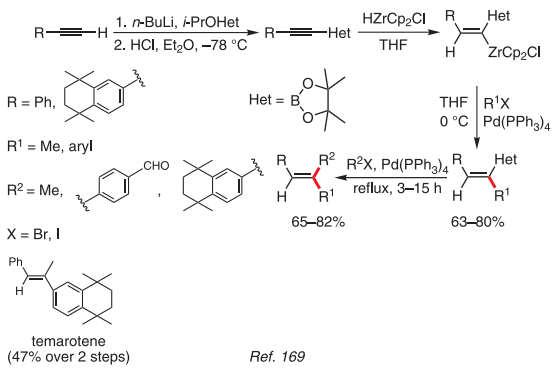

**Scheme 13**. Pd-Catalyzed Selective and Stepwise Disubstitution of 1,1-Dihalo-1-alkenes with Organozincs.



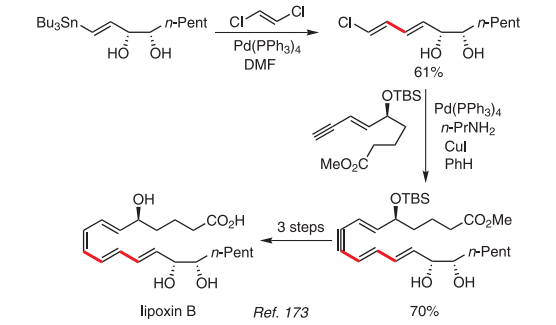

**Scheme 14**. Pd-Catalyzed *E*⇌*Z* Isomerization of 2-Pallado-1,3-dienes.



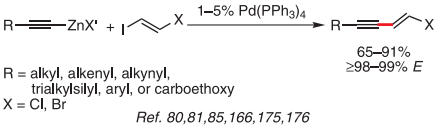

**Scheme 15**. The Pd-Catalyzed, Strictly "Pair-Selective", Two-Step Synthesis of Unsymmetrically Substituted Conjugated Diynes.



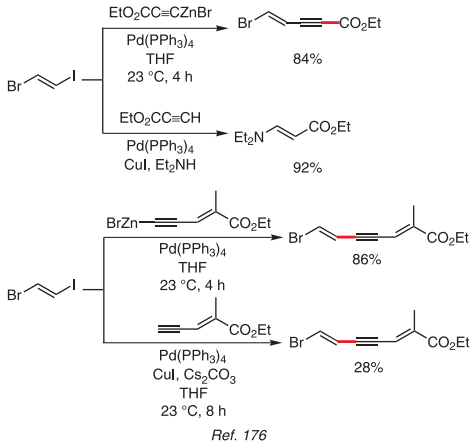

**Scheme 16**. The Pd-Catalyzed Two-Stage Cross-Coupling with 1-Bora-1-zircona-1-alkenes.




**Scheme 17**. The Synthesis of Lipoxin B via a Pd-Catalyzed Alkenylation and Alkynylation of (*E*)-ClCH=CHCl.




**eq 6**




**Scheme 18**. Comparison of the Negishi and Sonogashira Coupling Reactions in the Pd-Catalyzed Alkynylation of (*E*)-BrCH=CHI.

excess (≤5 equiv) of the 1,2-dihaloethylene was typically needed to attain high monosubstitution and/or trans-selectivity levels. Nonetheless, some of these reactions appear to be highly promising, as suggested by the synthesis of lipoxin B (**Scheme 17**).[173] Also attractive and promising are some cyclization reactions via Pd-catalyzed alkynyl–alkenyl coupling using (*Z*)-ClCH=CHCl.[15,174] The discussion in this section will focus, however, on the use of (*E*)-ClCH=CHI, (*E*)-BrCH=CHI, and (*E*)-BrCH=CHC≡CSiMe$_3$, which is derived from (*E*)-BrCH=CHI.

### 3.3.1. Pd-Catalyzed Selective Monosubstitution of (*E*)-2-Chloro- and (*E*)-2-Bromo-1-iodoethenes

The presence of the second halogen atom in 1,2-dihalo-1-alkenes renders these compounds significantly more reactive than ordinary monohaloalkenes in their Pd-catalyzed monosubstitution reactions. Less well appreciated is that the second substitution of the monosubstitution products derived from 1,2-dihaloalkenes is also substantially more favorable than the corresponding reaction of the same monohaloalkenes in their free alkene forms. After all, the initial products of monosubstitution are monohaloalkene–Pd complexes ready for the second oxidative addition via a strictly intramolecular process. For these reasons, any of the 1,2-dihalo-1-alkenes containing Cl, Br, and/or I are sufficiently reactive in the Pd-catalyzed cross-coupling. Indeed, the main concern in their Pd-catalyzed monosubstitution is how to prevent an unwanted second substitution. This is precisely the reason why a large excess of ClCH=CHCl is commonly used to minimize unwanted disubstitution. Although not fully established, this difficulty may be expected to be further magnified in the cases of BrCH=CHBr and ICH=CHI. Little, if any, is known about BrCH=CHCl. In ClCH=CHI, two carbon–halogen bonds are maximally differentiated, and monosubstitution of the iodine is expected to be more favorable. On the other hand, the second substitution of the chloroalkene products with a different organometal than the one used for the first substitution is generally less favorable than the corresponding reaction of bromoalkenes. In this respect, BrCH=CHI is a more desirable reagent than ClCH=CHI. It would be advantageous to consider both BrCH=CHI and ClCH=CHI and then compare the overall results for optimization. In cases where the cost of these 1,2-dihaloethylenes is a significant factor, ClCH=CHCl may also be tested and compared. In contrast to the Pd-catalyzed cross-coupling of ordinary monohaloalkenes, the corresponding monosubstitution of 1,2-dihaloethylenes has proved to be generally much more capricious and unpredictable. Nevertheless, the Pd-catalyzed monoalkynylation of (*E*)-ClCH=CHI and (*E*)-BrCH=CHI has been developed into a dependable and widely applicable reaction (**eq 6**).[80,81,85,166,175,176] In this regard, some striking differences between the use of alkynylzincs and terminal alkynes containing electron-withdrawing groups should be noted (**Scheme 18**).[176]

As expected, the Pd-catalyzed alkenylation of (*E*)-ClCH=CHI was favorable,[60,79] but the corresponding reaction of (*E*)-BrCH=CHI required extensive optimization. After screening many catalysts and reaction parameters, a set of parameters consisting of $InCl_3$ (≤0.34 equiv), 1% Pd(DPEphos)$Cl_2$, 2% DIBAL-H, 2% TFP, and THF was found to be almost uniquely satisfactory (yields of the monoalkenylated products ranged from 77 to 91%).[60] This has also been applied to the related arylation; however, the corresponding alkylation has not been satisfactory.

The 1-chloro- and 1-bromoalkenes, obtained as described in the preceding two paragraphs, rarely represent the final natural products. However, pitiamide A is one such rare example, which has been prepared by using this approach.[79]

### 3.3.2. Pd-Catalyzed Second-Stage Substitution Reactions of Alkenyl Chlorides and Bromides, and the One-Pot Tandem Disubstitution of 1,2-Dihaloethylenes

Even though 1-chloro-1-en-3-ynes and 1-chloro-1,3-dienes, obtained as described in Section 3.3.1, are considerably more reactive than 1-chloro-1-monoenes in the Pd-catalyzed cross-coupling due to the presence of conjugated π bonds, their Pd-catalyzed cross-coupling reactions are significantly more sluggish than the corresponding reactions of their bromo analogs. Nevertheless, a highly satisfactory (71–97% yields) set of conditions has recently been found for their alkylation and arylation.[177] It consists of the use of alkyl- or arylmagnesium halides, $ZnCl_2$ (0.6 equiv), 5% $Pd(dppf)Cl_2$, and THF at reflux temperature. This development has significantly elevated the synthetic value of (*E*)-ClCH=CHI and (*E*)-ClCH=CHCl vis-à-vis (*E*)-BrCH=CHI.

The Pd-catalyzed disubstitution of (*E*)-ClCH=CHI and (*E*)-BrCH=CHI can be achieved without isolation of the monosubstitution products, as exemplified by the Pd-catalyzed one-pot dialkynylation.[176] Construction of the pentaenediyne framework of xerulin was achieved by a Pd-catalyzed two-step alkynylation–alkenylation.[80] A similar Pd-catalyzed alkynylation–alkenylation of (*E*)-BrCH=CHI has been applied to the synthesis of *cis*- and *trans*-bupleurynols (**Scheme 19**).[85]

A useful variation of the Pd-catalyzed alkynylation–alkenylation of (*E*)-BrCH=CHI is to use its C–I bond as an electrophile but convert the C–Br bond into a nucleophilic C–Zn bond, as in the preparation of ethyl 2-methyl-2,4-heptadien-6-ynoate, a key intermediate in the synthesis of 6,7-dehydrostipiamide.[87]

### 3.3.3. Iterative Carbon–Carbon-Bond Formation by the Pd-Catalyzed Cross-Coupling of 1,2-Dihaloethylenes and 1-Halo-1-buten-3-ynes

1,2-Dihaloethylenes and 1-halo-1-buten-3-ynes discussed above can be used as two- and four-carbon synthons, respectively, for the iterative construction of carbon skeltons containing repeating units derived from them. In the synthesis of xerulin,[80] an iterative process was utilized to synthesize a bromodiendiyne as a key intermediate. It should also be noted that this procedure can, in principle, be iterated as many times as desired. Although this process has not yet been applied to the synthesis of conjugated triynes or higher oligoynes, it has been employed for the synthesis of various conjugated diynes.[165,166] It is a satisfactory and strictly "pair-selective" method, but a potentially more economical diyne synthesis, shown in Scheme 15, could prove to be more economical in most cases.

One highly attractive application of (*E*)-1-bromo-4-trimethylsilyl-1-buten-3-yne is to use it as a four-carbon synthon for the iterative construction of conjugated oligoenes including oligoene macrolides, carotenoids, and retinoids. A highly efficient, selective, and general method for the synthesis of conjugated (*all-E*)-oligoenes of type $(CH=CH)_n$ via an iterative tandem hydrozirconation–palladium-catalyzed cross-coupling has recently been developed (**Scheme 20**).[178] It promises to be applicable to the efficient synthesis of various oligoene macrolides.[179]

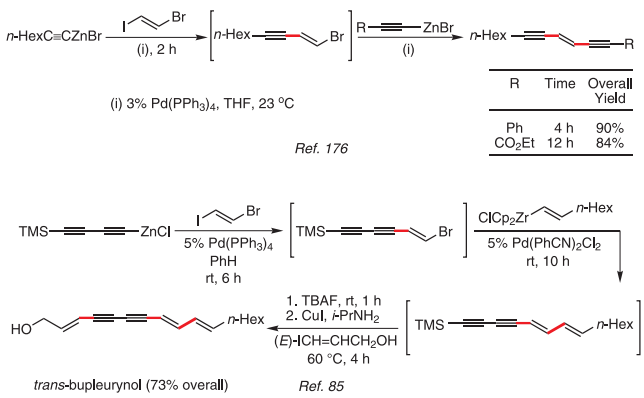
A related iterative carboalumination–cross-coupling process has also been developed and applied to the synthesis of both symmetrical and unsymmetrical carotenoids as well as retinoids.[81] It is not only highly efficient but also ≥98–99% stereoselective, even after incorporation of several stereodefined trisubstituted alkene units along with similar numbers of disubstituted alkene units.

### 3.3.4. 1,2-Dimetalloethylenes, 1-Metallo-2-haloethylenes, and Other Related Alkene Synthons

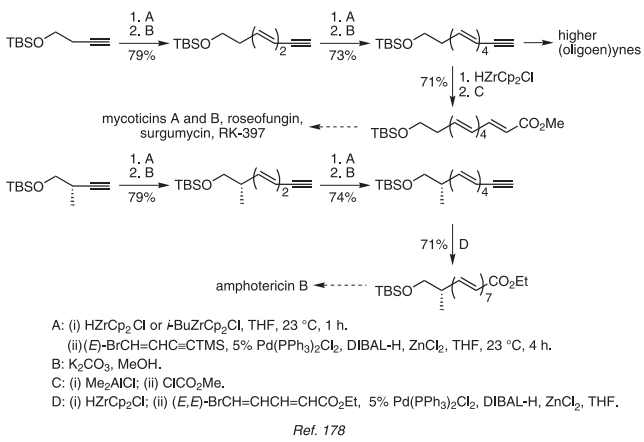
A number of classes of 1,2-dimetalloethylenes and 1,2-dimetallo-1-alkenes are conceivable, and some of those that contain Zn, B, Si, and Sn were briefly discussed in Section 2.2.1.[1a] In Scheme 1, (*E*)-$Bu_3SnCH=CHZnCl$ is shown to be far superior to (*E*)-$Bu_3SnCH=CHSnBu_3$ in the Pd-catalyzed reaction with methyl (*E*)-3-bromo-2-methylacrylate.[30] A related (*all-E*)-1,3,5-hexatriene derivative was recently used to synthesize xerulinic acid (**Scheme 21**).[88]

## 4. Conclusions

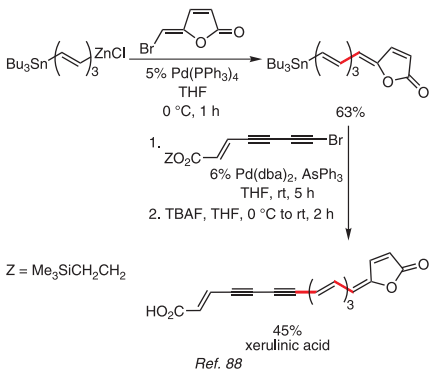
- Since the discovery of the Pd-catalyzed alkenylation by the Negishi coupling in the mid-1970s,[16–18,21–24] it has been extensively developed into a widely applicable, highly selective, and generally satisfactory method for the synthesis of alkenes by attaching a C–C single bond onto a C=C moiety.
- Generally speaking, zinc offers a very desirable combination of (i) high reactivity under the Pd-catalyzed conditions and (ii) a surprisingly favorable chemoselectivity profile. Furthermore, zinc salts, such as $ZnCl_2$ and $ZnBr_2$, can be used as promoters in the Pd-catalyzed cross-coupling reactions of other organometals including those containing Li, Mg, B, Al, Sn, Cu, and Zr primarily through transmetallation to Zn (Scheme 1). This has effectively expanded the scope of the Pd-catalyzed organozinc cross-coupling. In some cases of alkenylation with alkenylmetals containing Al and Zr, however, $InCl_3$ and $InBr_3$ can be more favorable promoters than Zn salts.[60] It is also worth noting that organomagnesiums, which are generally inferior to the corresponding organozincs, may prove to be superior to the latter, as suggested by recent results obtained with certain alkenyl chlorides.[29] It is not inconceivable that the hard and soft acids and bases principle is operative in the Pd-catalyzed cross-coupling as well.
- Until recently, the great majority of the Negishi coupling examples had been carried out in the presence of Pd catalysts containing $PPh_3$, TFP, dppf, and dppp. More recent studies have indicated that those containing DPEphos, trialkylphosphines (e.g., $P(t\text{-}Bu)_3$, $PCy_3$, $PCyp_3$), and 2-dialkylphosphinobiphenyls, as well as some non-phosphine ligands, are not only useful in many demanding cases, but also complementary among themselves (Figure 1 and Schemes 13 and 14). It is important to note that, although these structurally more varied and/or complex ligands will add to the cost of carrying out the Pd-catalyzed cross-coupling, higher costs of ligands and catalysts can be offset by more favorable results, in particular by higher turnover numbers (TONs). In this context, it is encouraging to learn from recent studies that the TONs in the Pd-catalyzed cross-couplings, including the Negishi coupling, can generally and readily reach the $10^3$–$10^5$ levels and even the $>10^6$ levels in some cases.[61]
- Of the sixteen cross-coupling combinations for the Pd-catalyzed alkenylation discussed throughout this article, only four classes of reaction, namely allyl–alkenyl, propargyl–alkenyl, enoxy–alkenyl, and alkenyl–alkyl coupling reactions remain underdeveloped. Fortunately, allyl–alkenyl, propargyl–alkenyl, and alkenyl–alkyl coupling reactions may be substituted with the corresponding alkenyl–allyl, alkenyl–propargyl, and alkyl–alkenyl coupling reactions to attain the same synthetic goals in most cases. α Alkenylation of carbonyl compounds can also be achieved via the Pd-catalyzed reaction of alkenylzincs with α-haloenones (Section 2.8). Thus, the




**Scheme 19**. The Pd-Catalyzed Dialkynylation and Alkynylation–Alkenylation of (*E*)-BrCH=CHI.




**Scheme 20**. The Synthesis of Conjugated Oligoenes via an Iterative Hydrozirconation–Cross-Coupling Tandem Process.




**Scheme 21**. The Synthesis of Xerulinic Acid via an Alkenyl–Alkenyl Coupling with (*all-E*)-6-Stanna-1,3,5-hexatrienylzinc Chloride.

Pd-catalyzed alkenylation can, in principle, be employed for the synthesis of all conceivable types of alkenes. The Pd-catalyzed alkenylation by the Negishi coupling is not only generally favorable in twelve out of sixteen cross-coupling combinations for the synthesis of alkenes, but also either the most satisfactory or one of the most satisfactory cross-coupling protocols known today along with the Pd-catalyzed alkenylation via alkenylborons (Suzuki coupling).[1,5,6] Some of the other currently known protocols involving Mg,[9,10] In,[11] Si,[1,12] and Cu[13] may also be further developed into widely used ones. Especially noteworthy are the alkenyl–alkenyl (Sections 2.3 and 3) alkynyl–alkenyl (Sections 2.4, 3.2, and 3.3), and alkyl–alkenyl (Sections 2.6, 3.1, and 3.2) couplings that currently appear to be most generally and satisfactorily achieved by the Negishi protocol.

- One of the advantages of the Pd-catalyzed alkenylation by the Negishi coupling is that Al, Zr, and Zn collectively offer various selective hydrometallation and carbometallation reactions, the products of which can be directly used for cross-coupling with minimal synthetic manipulations (Section 3.1).
- The previously underdeveloped and capricious stepwise disubstitution of 1,1-dihalo-1-alkenes has now been developed into a selective, predictable, and satisfactory synthetic method (Section 3.2). The use of organozincs in conjunction with $Pd(DPEphos)Cl_2$ and $Pd(dppf)Cl_2$ in the first substitution step and $Pd[(t\text{-}Bu)_3P]_2$ and related alkylphosphine-containing complexes in the second substitution step has been the key to recent successes in many cases. In the second substitution step of 2-halo-1,3-dienes, the use of $Pd(DPEphos)Cl_2$ and other conventional catalysts containing dppf, $PPh_3$, and so on has led to potentially useful and near-complete stereoinversion of the carbon–carbon double bond.[163]
- The Pd-catalyzed alkenylation discussed above has been significantly supplemented by the introduction of 1,2-dihaloethylenes and 1-halo-1-buten-3-ynes as two- and four-carbon synthons (Section 3.3). The combined use of 1-halo-1-buten-3-ynes and hydrometallation or carbometallation permits efficient and selective iterative syntheses of oligoenes including oligoene macrolides and carotenoids (e.g., Scheme 20).

## 5. Acknowledgments

The corresponding author (EN) wishes to dedicate this article to his lifelong mentor, the late Professor Herbert C. Brown, who passed away on December 19, 2004. His guidance and assistance over almost four decades (1966–2004) have played numerous positive and crucial roles in EN's career. Indeed, Professor Brown's suggestion to develop alkyne-hydroboration-based routes to prostanoids in the late 1960s turned EN's attention first to Cu–B, then to Ni–B, and eventually to Pd–Al, Zr, and Zn through Ni–Al, Zr, and Zn combinations during the 1972–1978 period at Syracuse University. Over 60 graduate students and postdoctoral associates have participated in this endeavor, and we are deeply indebted to their dedicated efforts. Although it is not practical to mention all of their names here, many of them are shown in pertinent references cited herein. EN is especially grateful to seminal contributions by the first four contributors, i.e., S. Baba, A. O. King, N. Okukado, and D. E. van Horn. This project at Purdue has been mainly supported by the National Science Foundation, the National Institutes of Health, and Purdue University including the H. C. Brown Distinguished Professorship Fund. Earlier support by the Research Corporation, the ACS Petroleum Research Fund, and Syracuse University is also gratefully acknowledged.

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**Qian Hu** graduated from Huazhong University of Science and Technology (China) in 2001 with an M.S. degree in applied chemistry. In 2002, she joined Professor Ei-ichi Negishi's group at Purdue University. In fulfilling a part of the requirements for the Ph.D. degree, she is currently conducting research on the total synthesis of natural products and the development of new synthetic methods in the area of transition-metal-catalyzed cross-coupling reactions.

**Zhihong Huang** was born in 1979 in Hubei Province, P. R. China. He obtained his B.S. degree in 2001 from the Department of Technical Physics at Peking University. Between 2001 and 2003, he was a member of Professor Jean-Luc Montchamp's group at Texas Christian University, where he received his M.S. degree in 2003. He then joined Professor Negishi's group at Purdue University, where he is currently working on the development of new synthetic methods that are based on transition-metal catalysis and in the area of natural product synthesis.

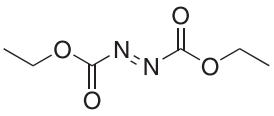
**Mingxing Qian** earned his Ph.D. degree in industrial catalysis in 2000 from Dalian University of Technology (China). From August 2001 to March 2005, he worked as a postdoctoral fellow at Purdue University, under the guidance of Professor Ei-ichi Negishi, on palladium-catalyzed carbon–carbon-bond-forming reactions and natural product synthesis. He is currently a postdoctoral research associate in Professor F. Gabbai's group at Texas A&M University, where he is carrying out research on the design, synthesis, and application of transition-metal complexes for olefin oligomerization and polymerization.

**Guangwei Wang** was born in 1976 in Henan Province, P. R. China. He received his B.S. degree from Lanzhou University in 1998. He then worked in Professor Shengming Ma's group until 2003 at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. In 2004, he enrolled at Purdue University to pursue his Ph.D. degree under the direction of Professor E. Negishi. His research interests include the development of new synthetic methods based on transition-metal catalysis and the synthesis of natural products.


# Diethyl Azodicarboxylate:
## *Back from the DEAD!*

- Widely used for aminations, cyclodehydrations, deoxygenations, and dehydrative alkylations.
- Is effective in the creation of new carbon–carbon bonds.
- Functions as a dienophile in [4+2] cycloadditions.[1]
- Serves as an activating agent in the silylation of alcohols.[2]
- Is a good Michael acceptor.[3]
- Reacts with secondary alcohols in the Mitsunobu reaction, providing a powerful method for the inversion of stereogenic centers.

Due to stricter safety regulations, shipment of DEAD as a dry reagent is prohibited in the U.S. Sigma-Aldrich recently achieved full compliance with UN and U.S. DOT safety regulations, and is proud to offer this versatile reagent for your research needs as a stable and safe 40% solution in toluene.



| | | | |
|---|---|---|---|
| NEW | **563110** | Diethyl azodicarboxylate solution, 40 wt. % in toluene | 100 g |
| | **561851** | Diethyl azodicarboxylate, polymer-bound, 1% DVB, 100–200 mesh | 5 g<br>25 g |



**References**

(1) (a) Kuethe, J. T.; Davies, I. W. *Tetrahedron Lett.* **2004**, *45*, 4009. (b) Ellis, J. M.; King, S. B. *Tetrahedron Lett.* **2002**, *43*, 5833. (2) Hayashi, M. et al. *Tetrahedron Lett.* **2004**, *45*, 1409. (3) Comelles, J. et al. *J. Org. Chem.* **2004**, *69*, 6834.

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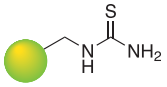
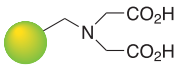
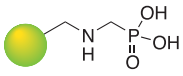
# QuadraPure™ Metal Scavengers

## *Sigma-Aldrich is pleased to announce an agreement with Reaxa Ltd. to distribute QuadraPure™ metal scavengers worldwide.*

The QuadraPure™ functionalized macroporous and microporous resins are intended to solve problems associated with 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 in larger quantities.**

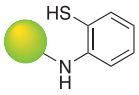
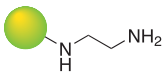
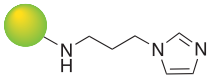
## Macroporous Resins

| Cat. No. | Name | Structure | Typical Experimental Capacity | Metals Removed | Effective in Acid/Base? |
|---|---|---|---|---|---|
| **655422** | **QuadraPure™ TU**<br>400–600 µm |  | 0.19 mmol/g<br>(based on $Pd(OAc)_2$ in $CH_2Cl_2$) | Pd, Pt, Ru, Au, Ag, Cu, Ni, Zn, Hg, Pb, and Cd | Y/Y |
| **657026** | **QuadraPure™ IDA**<br>350–750 µm |  | 0.16 mmol/g<br>(based on $Cu(acac)_2$ in $CH_2Cl_2$) | Fe, Al, Ga, In, Cu, V, Pb, Ni, Zn, Cd, Be, Mn, Ca, Mg, Sr, and Ba | Y[a]/Y |
| **657611** | **QuadraPure™ AMPA**<br>350–750 µm |  | 0.17 mmol/g<br>(based on $Ni(acac)_2$ in $CH_2Cl_2$) | Fe, Cu, Ni, Pb, V, Al, Sn, Zn, Cd, Co, Pd, Ca, Mg, Sr, and Ba | Y[a]/Y |

[a] pH < 2 gives poor scavenging.

## Microporous Resins

They possess excellent scavenging properties, particularly for palladium, at different pH values, and in the presence of competing ligands and substrates. The metal loading capacity can be significantly higher for these microporous products.

| Cat. No. | Name | Structure | Functional Group Loading | Metals Removed | Effective in Acid/Base? |
|---|---|---|---|---|---|
| **657662** | **QuadraPure™ MPA**<br>100–400 µm |  | 1.5 mmol/g | Pd, Ru, Rh, Hg, Au, Ag, Cu, Pb, Ir, Pt, Cd, Co, and Sn | Y/Y |
| **657646** | **QuadraPure™ AEA**<br>100–400 µm |  | 1.3 mmol/g | Pd, Sn, Ru, Pt, Ni, Cu, Zn, and Co | N/Y |
| **657654** | **QuadraPure™ IMDAZ**<br>100–400 µm |  | 1.5 mmol/g | Ni, Pd, Os, Rh, Co, V, Fe, Cu, and Sn | N/Y |

To inquire about larger quantities for any of the products listed above, please call 800-244-1173 (USA) or visit us at **www.safcglobal.com**.

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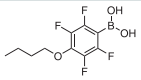
# More New Products from Aldrich R&D

## Boronic Acids and Esters

### 4-Butoxy-2,3,5,6-tetrafluorophenylboronic acid

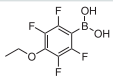
**657255**
$C_{10}H_{11}BF_4O_3$



2 g
10 g

### 4-Ethoxy-2,3,5,6-tetrafluorophenylboronic acid

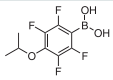
**657298**
$C_8H_7BF_4O_3$



2 g
10 g

### 4-Isopropoxy-2,3,5,6-tetrafluorophenylboronic acid

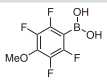
**657263**
$C_9H_9BF_4O_3$



2 g
10 g

### 4-Methoxy-2,3,5,6-tetrafluorophenylboronic acid

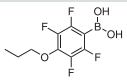
**657301**
$C_7H_5BF_4O_3$



2 g
10 g

### 4-Propoxy-2,3,5,6-tetrafluorophenylboronic acid

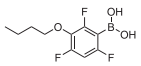
**657271**
$C_9H_9BF_4O_3$



2 g
10 g

### 3-Butoxy-2,4,6-trifluorophenylboronic acid

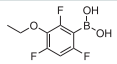
**657352**
$C_{10}H_{12}BF_3O_3$



1 g
5 g

### 3-Ethoxy-2,4,6-trifluorophenylboronic acid

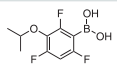
**657247**
$C_8H_8BF_3O_3$



1 g
5 g

### 3-Isopropoxy-2,4,6-trifluorophenylboronic acid

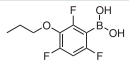
**657360**
$C_9H_{10}BF_3O_3$



1 g
5 g

### 3-Propoxy-2,4,6-trifluorophenylboronic acid

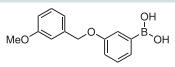
**657379**
$C_9H_{10}BF_3O_3$



1 g
5 g

### 3-(3′-Methoxybenzyloxy)phenylboronic acid

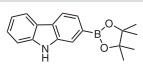
**657395**
$C_{14}H_{15}BO_4$



2 g
10 g

### 2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-9*H*-carbazole, 90%

**655724**
$C_{18}H_{20}BNO_2$

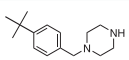


1 g
5 g

## Heterocyclic Building Blocks

### 1-(4-*tert*-Butylbenzyl)piperazine 97%

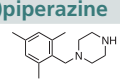
**650129**
$C_{15}H_{24}N_2$



1 g
5 g

### 1-(2,4,6-Trimethylbenzyl)piperazine

**651680**
$C_{14}H_{22}N_2$



1 g
5 g

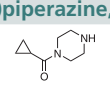
### 1-(Ethanesulfonyl)piperazine, 97%

**653306**
$C_6H_{14}N_2O_2S$

1 g
5 g

### 1-(Cyclopropanecarbonyl)piperazine, 97%

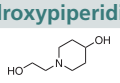
**653314**
$C_8H_{14}N_2O$



1 g
5 g

### 1-(2-Hydroxyethyl)-4-hydroxypiperidine, 96%

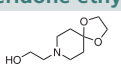
**655732**
$C_7H_{15}NO_2$



1 g
5 g

### 1-(2-Hydroxyethyl)-4-piperidone ethylene ketal, 97%

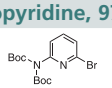
**655775**
$C_9H_{17}NO_3$



1 g
5 g

### 6-(Di-Boc-amino)-2-bromopyridine, 97%

**655848**
$C_{15}H_{21}BrN_2O_2$



5 g
25 g

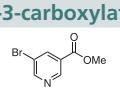
### Lithium 3-fluoropyridine-2-carboxylate, 90%

**656348**
$C_6H_3LiFNO_2$

1 g
5 g

### Methyl 5-bromopyridine-3-carboxylate, 97%

**657425**
$C_7H_6BrNO_2$



5 g

### 2,6-Dimethoxypyridine-3-carboxaldehyde

**657468**
$C_8H_9NO_3$

1 g
5 g

### 2-Acetyl-4-methylthiazole, 97%

**656313**
$C_6H_7NOS$

1 g
5 g

### 6-Isopropyl-1*H*-indole

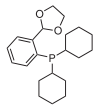
**655341**
$C_{11}H_{13}N$

1 g
5 g

## Organic Reagents and Building Blocks

### 2-(2′-Dicyclohexylphosphinophenyl)-1,3-dioxolane, 97%

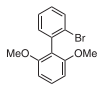
**655406**
$C_{21}H_{31}O_2P$



1 g

### 2′-Bromo-2,6-dimethoxybiphenyl, 97%

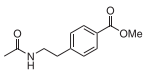
**655481**
$C_{14}H_{13}BrO_2$



5 g

### Methyl 4-(*N*-acetyl-2-aminoethyl)benzoate

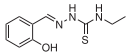
**656127**
$C_{12}H_{15}NO_3$



5 g

### 2-Hydroxybenzaldehyde *N*-ethylthiosemicarbazone, 97%

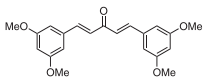
**657956**
$C_{10}H_{13}N_3OS$



1 g
10 g

### (1*E*,4*E*)-1,5-Bis(3,5-dimethoxyphenyl)-1,4-pentadien-3-one, 97%

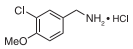
**656852**
$C_{21}H_{22}O_5$



1 g
5 g

### 3-Chloro-4-methoxybenzylamine hydrochloride

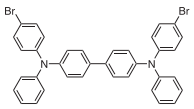
**657441**
$C_8H_{11}Cl_2NO$



5 g

### 4,4′-Bis[(4-bromophenyl)phenylamino)]biphenyl

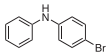
**656674**
$C_{36}H_{26}Br_2N_2$



1 g

### 4-Bromodiphenylamine, 97%

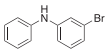
**657158**
$C_{12}H_{10}BrN$



1 g
5 g

### *N*-(3-Bromophenyl)aniline, 97%

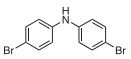
**654248**
$C_{12}H_{10}BrN$



1 g
10 g

### Bis(4-bromophenyl)amine

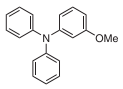
**657131**
$C_{12}H_9Br_2N$



5 g
25 g

### 3-Methoxytriphenylamine, 97%

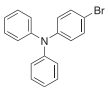
**640549**
$C_{19}H_{17}NO$



1 g
5 g

### 4-Bromo-*N*,*N*-diphenylaniline, 97%

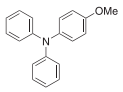
**643831**
$C_{18}H_{14}BrN$



5 g
25 g

### 4-Methoxy-*N*,*N*-diphenylaniline, 97%

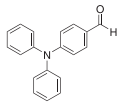
**646121**
$C_{19}H_{17}NO$



1 g
10 g

### 4-(Diphenylamino)benzaldehyde, 97%

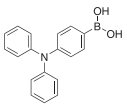
**647209**
$C_{19}H_{15}NO$



1 g
5 g

### 4-(Diphenylamino)phenylboronic acid

**647292**
$C_{18}H_{16}BNO_2$



1 g
5 g

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# Enantiopure Sulfoxides and Sulfinamides: Recent Developments in Their Stereoselective Synthesis and Applications to Asymmetric Synthesis


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## Outline



## 1. Introduction

In recent years, several new methodologies for the asymmetric synthesis of enantiopure sulfoxides and sulfinamides have emerged. The incentive for such prolific research lies in the numerous synthetic applications of these functional groups. Chiral sulfinamides have proven highly efficient as chiral auxiliaries in the synthesis of chiral amines[1] and as ligands in catalytic asymmetric reactions.[2] Chiral sulfoxides, themselves a target functionality in biologically active compounds,[3] have also been widely utilized as

chiral auxiliaries for asymmetric C–C-bond formation,[4] as ligands in catalytic asymmetric processes,[5] and in molecular recognition studies.[6] Despite numerous reports on the preparation of sulfinamides and sulfoxides, a general, practical, and economical approach to these valuable functionalities was still lacking until recently. The present review highlights the latest developments in the synthesis and application of sulfoxides and sulfinamides.

## 2. Asymmetric Synthesis of Chiral Sulfoxides and Sulfinamides

### 2.1. Background

The wide variety of methods for preparing optically active sulfoxides belong to either of two distinct approaches: asymmetric oxidation of prochiral sulfides[7] and organometallic addition to electrophilic sulfoxides with inversion of configuration at the sulfur atom.[8] This review will focus on recent advances in the latter approach.[9] The synthesis of unsymmetrical sulfoxides was originally carried out by Gilman in 1926.[10] In 1962, Andersen reported the first chiral sulfinyl transfer agent, (*S*)-menthyl *p*-toluenesulfinate (**1a**), which was used to prepare sulfoxides by addition of organometallics to the S–O bond of **1a** in high yield and excellent enantioselection, albeit with a limited scope.[11] The Andersen method was extended to other chiral alcohols[12] such as **1b**.[13] Khiar, Fernández, Alcudia, and co-workers developed an elegant preparation of optically active sulfoxides and sulfinamides from racemic aryl or alkyl sulfinyl chlorides using diacetone D-glucose as a chiral controller.[13] In 1972, Wudl and Lee disclosed the first cyclic sulfinyl transfer agent, an (–)-ephedrine-derived 1,2,3-oxathiazolidine-2-oxide (**2**), which was utilized to prepare methyl aryl sulfoxides.[14] Later, Hiroi employed the same type of technology using a chiral benzoxathiazine derivative that produced optically active sulfoxides.[15] However, sulfoxides obtained from ephedrine-based oxathiazolidines had low enantioselectivities and yields.[14,15] Use of trimethylaluminum as an additive was required to cleave the unactivated S–N bond and to produce sulfoxides in good yields and high enantioselectivities, except for hindered sulfoxides, such as *tert*-butyl sulfoxides.[16] To overcome these difficulties, Kagan introduced cyclic sulfite **3**, which led to a mixture of regioisomeric sulfinate esters upon treatment with a variety of organometallic compounds.[17] Treatment of the purified sulfinate esters with a second organometallic agent produced chiral sulfoxides in excellent enantioselectivities and good yields (**Figure 1**).

Evans's *N*-sulfinyloxazolidinone **4** and, more recently, Oppolzer's *N*-sulfinylsultam **5** produced chiral sulfoxides in high enantioselectivities;[18,19] but these chiral sulfinyl transfer agents were mostly limited to the preparation of aryl sulfoxides. Later on, Ellman synthesized the optically pure *tert*-butyl *tert*-butanethiosulfinate (**6**) and utilized it for the production of a variety of *tert*-butyl sulfoxides in excellent enantioselectivities and high yields.[20] A number of other methodologies for the preparation of optically active sulfoxides have also emerged, but they still lack generality.[21] Recently, Senanayake and co-workers introduced the N-activated 1,2,3-oxathiazolidine-2-oxide derivatives **7**, which enabled the highly general, selective, and practical synthesis of a wide range of chiral sulfoxides and sulfinamides in high yields and excellent enantioselectivities (**Scheme 1**).[22] The key to the success of this new technology resides in the utilization of readily available activated amino alcohols and thionyl chloride to build the novel and reactive sulfinyl transfer agents **7**.

### 2.2. Preparation of Sulfoxides

Three decades ago, Wudl and Lee demonstrated the utility of (–)-ephedrine-derived 1,2,3-oxathiazolidine-2-oxide **2** for the enantioselective synthesis of chiral sulfoxides. When **2** was subjected to carbon nucleophiles, the reactive S–O bond was cleaved selectively and produced *N*-methylsulfinamides. Addition of a second carbon nucleophile displaced the S–N bond of these acyclic sulfinamides and led to optically active sulfoxides. However, this second displacement resulted in poor enantioselectivities and yields (**Scheme 2**).[14]

Senanayake and co-workers reasoned that electron-donating groups, such as methyl, on the nitrogen of the oxathiazolidine oxide would strengthen the S–N bond, while weakening the S–O bond of **2**.[23] Thus, substituting an electron-withdrawing group for the methyl group on the nitrogen should act as an activator and reverse the bond strengths and order of bond cleavage (S–N before S–O) (**Figure 2**).[22a]

To test this hypothesis, Senanayake's group chose to utilize an arylsulfonyl group as a nitrogen-activating group and the indan platform as the conformationally constrained backbone. Synthetic investigations aimed at preparing the required 1,2,3-oxathiazolidine-2-oxide starting materials indicated that the base–solvent combination used in the reaction of aminoindanol **12** with $SOCl_2$ had a pronounced effect on the endo/exo ratio of the product, **13** (**eq 1**).[22b] After extensive base screening, it was determined that using Ar = 2,4,6-mesityl and 3,5-lutidine as base in THF gave the best endo/exo selectivity of 97:3. The high endo selectivity was switched to a high exo selectivity by a simple change in the pyridine substitution pattern. Thus, using sterically congested 2,6-di-*tert*-butylpyridine led to 2:98 (Ar = 4-tolyl) and 7:93 (Ar = 2,4,6-mesityl) endo/exo selectivities. After recrystallization, both endo and exo isomers of **13** were prepared in kilogram quantities from one enantiomer of the indan platform in diastereomerically and enantiomerically pure forms.

To illustrate the power of this approach, treatment of either *endo*- or *exo*-**13a** (Ar = 2,4,6-mesityl) with *tert*-butylmagnesium chloride at low temperature led to the chemoselective cleavage of the S–N bond in each to produce the corresponding diastereomers of sulfinate **14** in >90% yields and with inversion of configuration at the sulfur atom (**Scheme 3**).[22b] Upon treatment with *i*-PrMgCl, the individual diastereomeric sulfinate, **14**, provided the corresponding enantiomer of *tert*-butyl isopropyl sulfoxide (**15**)—with inversion of configuration at the sulfur atom—in excellent yield and with outstanding recovery of enantiopure **12a** (>96%).

Other *N*-sulfonylamino alcohols were also evaluated as oxathiazolidine oxide precursors. Inexpensive and readily available *N*-toluenesulfonylnorephedrine, (*R,S*)-**16**, was found to be an ideal template for the preparation of *N*-toluenesulfonyl-4-methyl-5-phenyl-1,2,3-oxathiazolidine-2-oxide (TMPOO, **17**). Similarly to **13**, oxathiazolidine oxide **17** was subjected to successive nucleophilic attacks on the sulfur atom in order to evaluate the scope of the methodology (**Scheme 4**).[22b] It was discovered that the S–N bond of TMPOO could also be cleaved with mild reagents such as organozincs of sterically congested halides to give the sulfinate intermediates. In addition to alkyl–alkyl chiral sulfoxides, this powerful process gave access to either enantiomer of alkyl–aryl and aryl–aryl sulfoxides. Finally, *tert*-butyl (*tert*-butanesulfinyl)acetate and diethyl (*tert*-butanesulfinyl)methylphosphonate were generated by addition of the appropriate lithium reagent to the corresponding *tert*-butanesulfinate, which demonstrated the ability of this methodology to access a variety of novel structures and possibly lead to new biological targets.[22b]

### 2.3. Preparation of Sulfinamides

Pioneering work by Davis and co-workers underlined the importance and utility of enantiomerically pure sulfinamides as

building blocks in the asymmetric synthesis of amine derivatives.[1] Davis's *p*-toluenesulfinamide (**19**), prepared from Andersen's menthyl ester **1a**, was condensed with aldehydes and ketones to produce chiral sulfinyl imines (**Scheme 5**).[24] The sulfinyl group not only stabilized imines, but also activated them toward addition of a wide range of nucleophiles. Furthermore, the chiral substituent on the imine nitrogen provided high diastereofacial selectivity for nucleophilic addition on the imine carbon, leading to chiral sulfinamides **21**. The sulfinyl group was readily cleaved by brief treatment with acid, thus providing a very general approach for the asymmetric synthesis of a broad range of amine-containing compounds.[1,2,24]

Ellman and co-workers later demonstrated the overall differences between the *tert*-butanesulfinyl and the *p*-toluenesulfinyl groups. Interestingly, *tert*-butanesulfinamide proved more nucleophilic than *p*-toluenesulfinamide in the direct condensation with aldehydes and ketones. It was also more stereo- and regioselective upon nucleophilic attack, because of the greater steric hindrance and electron-donating properties of the *tert*-butyl as compared to those of the *p*-tolyl group.[25]

The asymmetric oxidation of di-*tert*-butyl disulfide (**22**), using hydrogen peroxide with $VO(acac)_2$ and ligand **23**, proceeded in high yield and enantioselectivity. Displacement of *tert*-butylthiolate from intermediate **24** with lithium amide provided *tert*-butanesulfinamide (**25**) in an analytically and enantiomerically pure form by crystallization (**Scheme 6**).[25] Application of this method to the preparation of other sulfinamides has not been reported.

Senanayake and co-workers extended their strategy for the preparation of chiral sulfoxides to the synthesis of *tert*-butanesulfinamide. Reaction of (1*R*,2*S*,*R*)-**14** or (1*R*,2*S*,*S*)-**14** with $Li/NH_3$/THF at –78 °C led to cleavage of the S–O bond with inversion of configuration at the sulfur atom, and gave rise to the corresponding enantiomers of *tert*-butanesulfinamide in quantitative yields. When the inexpensive oxathiazolidine oxide **17** was reacted first with *t*-BuMgBr and then with lithium amide, (*S*)-*tert*-butanesulfinamide was formed in 89% yield and 99% ee. A wide variety of structurally diverse tertiary alkyl and aryl sulfinamides were obtained with this double-inversion nucleophilic displacement strategy (**Scheme 7**).[23a]

Recently, Ellman and co-workers developed the first and unique multistep synthesis of a support-bound *tert*-butanesulfinamide derivative from enantiopure sulfinamide precursor (*S*)-**26g**.[26] However, the synthesis of (*S*)-**26g** required reduction of the benzylic position of a derivative of the chiral auxiliary (*S*)-2-amino-1,1,2-triphenylethanol. Thus, the expensive (*S*)-2-amino-1,1,2-triphenylethanol could not be recovered.[26] Using our approach, (*S*)-**26g** was prepared efficiently in excellent yield and optically pure form with efficient recovery of auxiliary (1*R,2S*)-**16**. The synthesis of a novel benzyl ether derived sulfinamide, (*S*)-**26h**, was also demonstrated. Sulfinamide (*S*)-**26h** and other ether-functionalized sulfinamides are potential precursors of ether-tethered, support-bound *tert*-butanesulfinamides.[27] This methodology has provided the first *modular* synthesis of this valuable family of enantiopure sulfinamides.

## 3. Chiral Sulfinyl Auxiliaries in Asymmetric Synthesis

Sulfinamides can be condensed with aldehydes and ketones to form *N*-sulfinyl imines in good yields. Nucleophilic addition followed by cleavage of the sulfinyl group leads to chiral primary amines. Davis and Ellman have used this method extensively to produce a variety of chiral amines using *p*-toluene- and *tert*-butanesulfinamides.[24,25] Recently, Ellman reported the highly diastereoselective

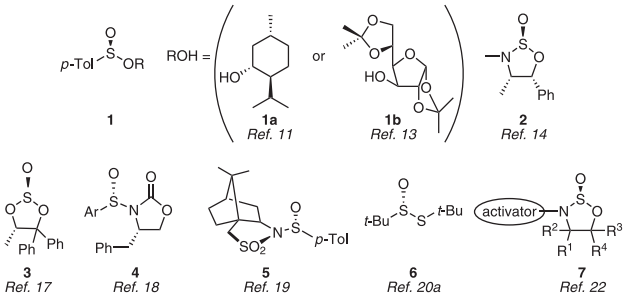
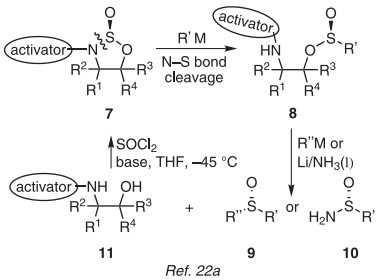
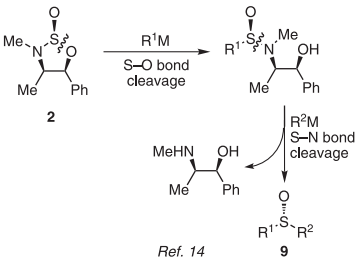



**Figure 1**. Selected Chiral Sulfinyl Transfer Agents.




**Scheme 1**. N-Activated Oxathiazolidine-2-oxides as Precursors of Chiral Sulfoxides and Sulfinamides.




**Scheme 2**. Wudl and Lee's Synthesis of Chiral Sulfoxides.

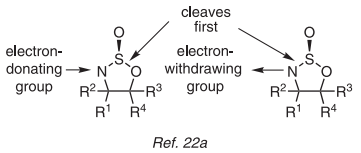
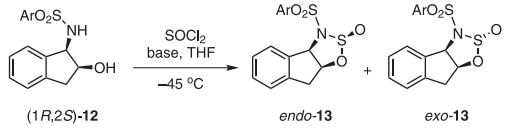


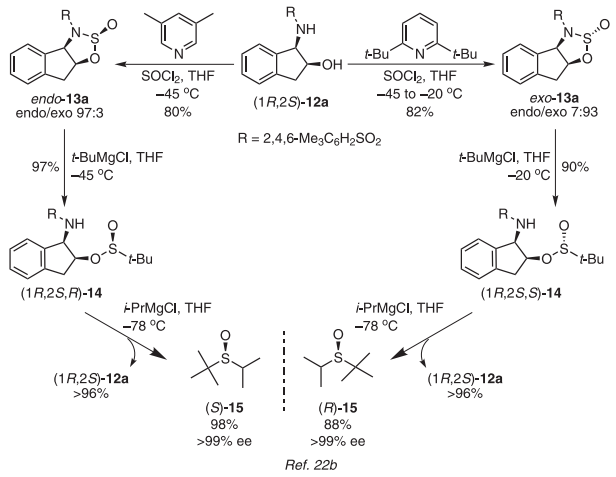

**Figure 2**. Activation Strategy for Oxathiazolidine Oxides.



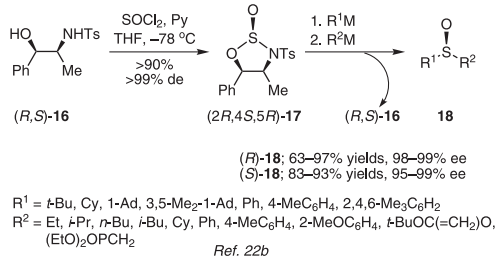

| SM | Ar | Base | 13 Yield | 13 Endo/Exo |
|---|---|---|---|---|
| **12a** | 2,4,6-mesityl | 3,5-lutidine | 80% | 97:03 |
| **12a** | 2,4,6-mesityl | 2,6-di-*t*-butylpyridine | 82% | 07:93 |
| **12b** | 4-tolyl | 2,6-di-*t*-butylpyridine | 85% | 02:98 |

*Ref. 22b*

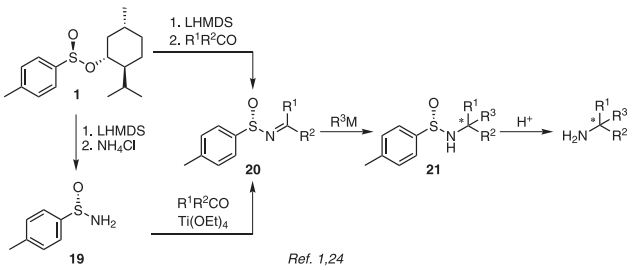
**eq 1**



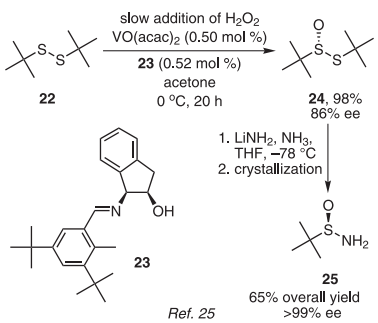

**Scheme 3**. Synthesis of Enantiomerically Pure (*R*)- and (*S*)-*tert*-Butyl Isopropyl Sulfoxides.




**Scheme 4**. Modular Asymmetric Synthesis of Enantiopure Sulfoxides.




**Scheme 5**. Asymmetric Synthesis and Reactions of *p*-Toluenesulfinyl Imines.




**Scheme 6**. Asymmetric Synthesis of *tert*-Butanesulfinamide.

addition of alkyl or aryl Grignard reagents to *N*-sulfinyl imines, **27**, derived from 3- and 4-substituted cyclohexanones (**eq 2**).[28] The reaction proceeded in good yields, but the selectivity appeared to be controlled by the cyclohexane ring substituents rather than the sulfinyl group stereochemistry. Therefore, *racemic tert*-butanesulfinamide was employed. Cleavage of the sulfinyl group in **28** provided α-substituted cyclohexylamines, a prevalent substructure in drugs and drug candidates.[28]

### 3.1. Synthesis of 1,2-Diamines

A novel, straightforward, and highly efficient synthesis of $C_2$-symmetrical vicinal diamines was developed very recently by Xu and co-workers (**Scheme 8**).[29] The homocoupling reaction of a variety of *N*-sulfinyl aldimines, **29**, proceeded smoothly using 2 equivalents of $SmI_2$ and 2 to 6 equivalents of HMPA in THF at –78 °C and produced the *d/l*-adducts, **30**, as single stereoisomers in moderate-to-high yields. Amine deprotection led to enantiopure $C_2$-symmetrical vicinal diamines, **31**. Davis and Deng reported an efficient asymmetric synthesis of both *syn*- and *anti*-α,β-diamino esters with high diastereoselectivities and good yields by addition of differentially N-protected glycine enolates to enantiopure sulfinyl imines and subsequent deprotection.[30]

### 3.2. Synthesis of Amino Alcohols

Senanayake and co-workers developed an efficient method for accessing *syn*- and *anti*-1,2-amino alcohols, as exemplified by the synthesis of *syn*-(3*R*,4*R*)-**35** and *anti*-(3*S*,4*R*)-**35** from a common *tert*-butanesulfinyl imine starting material, (*S*)-**32** (**Scheme 9**).[31] Good-to-excellent yields and high diastereoselectivities (>98%) were observed for the protected amino alcohol intermediates, **34**. Deprotection with HCl in methanol produced the corresponding enantiomerically enriched 1,2-amino alcohols in high yields.

A remarkable and general method for the asymmetric synthesis of *syn*- and *anti*-1,3-amino alcohols has recently been reported (**Scheme 10**).[32] The first application of metalloenamines derived from *N*-sulfinyl imines was reported for the highly diastereoselective addition to aldehydes. Reduction of the resulting β-hydroxy-*N*-sulfinyl imines, **37**, with catecholborane or $LiBHEt_3$ provided *syn*- and *anti*-1,3-amino alcohols with very high diastereomeric ratios. This method was found to be effective for a variety of imines and aldehydes. The convergent and efficient asymmetric syntheses of two natural products, (–)-8-epihalosaline and (–)-halosaline, were also accomplished.

Although addition of ester enolates to sulfinyl imines to afford β-amino esters has been well studied by Davis's and Ellman's groups, the diastereoselective addition of ketone enolates to *N*-sulfinyl imines has received much less attention. Recently, Davis and Yang reported a practical and elegant solution for the direct and highly diastereoselective asymmetric synthesis of β-amino ketones by addition of potassium enolates of methyl ketones to *N*-sulfinyl imines (**eq 3**).[33] Another very recent example of a highly diastereoselective synthesis of *syn*- and *anti*-1,3-amino alcohols has been reported by Nelson and co-workers.[34]

Senanayake and co-workers recently demonstrated that both enantiomers of 1,4-amino alcohols could be obtained from a single enantiomer of a sulfinyl imine, simply by changing the reaction solvent. Using THF as solvent, the addition of Grignard reagents (*R*)- or (*S*)-**44** to a common sulfinyl imine, (*R*)-**32**, allowed rapid access to the chiral amines with the *R* configuration at the amine carbons. In $CH_2Cl_2$, on the other hand, the same reactions led to the stereoisomers with the *S* configuration at the amine carbons (**Scheme 11**).[31] The observed reversed diastereoselectivity in $CH_2Cl_2$ and THF implies that the reaction may be taking place

through a chelated cyclic transition state in $CH_2Cl_2$ and a nonchelated acyclic transition state in THF. It has been postulated that different aggregation states of Grignard reagents in $CH_2Cl_2$ and THF might have an influence on the rate of the reaction.[31]

### 3.3. Synthesis of α-Amino Ketones

*N*-Sulfinyl-α-amino-1,3-dithioketals have recently been prepared in high de's and good yields by treating sulfinyl imines with lithio-1,3-dithianes. Selective removal of the *N*-sulfinyl or the thioketal groups affords stable α-amino-1,3-dithioketals or *N*-sulfinyl-α-amino ketones, respectively (**Scheme 12**).[35]

### 3.4. Synthesis of Amino Acids

The preparation of α-amino acids by asymmetric addition of cyanide to sulfinyl imines has been well documented by both Davis's and Ellman's groups.[36] Recently, Hou and co-workers described the reaction of chiral sulfinimines, derived from aliphatic aldehydes, with TMSCN in the presence of CsF under mild conditions. This CsF-promoted addition complements Davis's protocol. The addition gave α-amino nitriles with high diastereoselectivities (up to 98% de) and yields (92–99%) (**Scheme 13**).[36a] The formation of an intermediate *N*-sulfinyl enamine was suggested to play a crucial role in this TMSCN addition reaction. α,β-Diamino acid derivatives were also obtained in high diastereoselectivities (92–96% de) and yields (98%) from a similar reaction of 2-aziridinesulfinimines (R = *N*-benzylaziridin-2-yl) with TMSCN, followed by ring-opening of the aziridine ring in the α-aminonitrile intermediate with thiophenol.

The application of sulfinyl imines in the synthesis of β-amino acids from ester enolates has been well investigated independently by Davis, Ellman, and Adamczyk.[36b–e] This method is very general and allows access to a variety of β-substituted, α,β- and β,β-disubstituted, as well as α,β,β- and α,α,β-trisubstituted amino acids in high stereoselectivities.

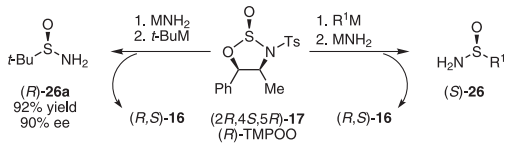
### 3.5. Synthesis of Aziridines

An efficient method for the preparation of enantiopure *N*-*tert*-butanesulfinyl aziridines was described by Chemla and Ferreira (**eq 4**).[37] Condensation of enantiopure *N*-*tert*-butanesulfinyl imines ($R_S$)-**49** with racemic allenylzinc bromide **50** afforded *trans*-ethynyl aziridines ($R_S$)-**51** in good-to-excellent yields and with excellent diastereoselectivities (>98%). The absolute stereochemistry of enantiopure ($R_S$)-**51** was shown to be ($R_S$,2*R*,3*R*) and to result from a chelation-type transition state in which the zinc atom of allenylzinc **50** coordinated both the nitrogen and the oxygen atoms of the sulfinyl imine. Removal of the *N*-*tert*-butanesulfinyl auxiliary of aziridines ($R_S$)-**51** by treatment with HCl in MeOH, led to the corresponding enantiomerically pure deprotected aziridines.[37]

Chiral, nonracemic vinyl aziridines have been conveniently prepared via a Darzens-type reaction between sulfinyl imines and α-haloenolates, which gave *cis*-*N*-sulfinylaziridine-2-carboxylates.[38] More recently, Stockman and co-workers reported a straightforward approach to the synthesis of a range of chiral alkyl and aryl vinyl aziridines, in high yields and excellent diastereoselectivities, by reaction of *tert*-butanesulfinyl imines with the ylide derived from *S*-allyltetrahydrothiophenium bromide (**eq 5**).[39]

### 3.6. Synthesis of α-Amino Phosphonates

Recently, Davis's group reported an asymmetric synthesis of *cis*-5-substituted pyrrolidine-2-phosphonates, which serve as proline surrogates (**Scheme 14**).[40] δ-Amino-α-diazo-β-ketophosphonates were synthesized from the corresponding *N*-sulfinyl-β-amino esters in five steps. Subsequent intramolecular metal carbenoid

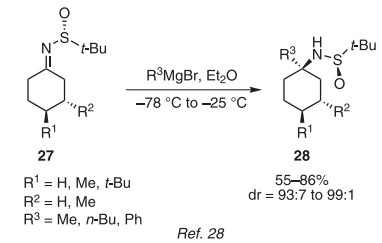



| 26 | $R^1$ | (*S*)-26 Yield[a] |
|---|---|---|
| **a** | *t*-Bu | 89% |
| **b** | $EtMe_2C$ | 90% |
| **c** | $Et_3C$ | 87% |
| **d** | 4-$MeC_6H_4$ | 83% |
| **e** | 2,4,6-$Me_3C_6H_2$ | 80% |
| **f** | 1-Ad | 80% |
| **g** | $(CH_2{=}CHCH_2CH_2)Me_2C$ | 90% |
| **h** | $(BnOCH_2CH_2)Me_2C$ | 85% |

[a] 99% ee in all cases, except for (*S*)-**26h**.

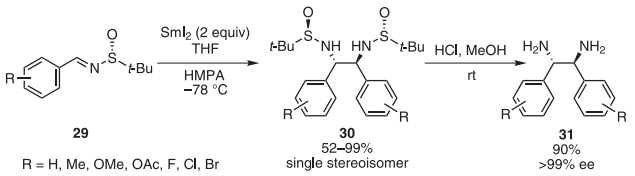
*Ref. 23a*

**Scheme 7**. Modular Asymmetric Synthesis of Enantiopure Sulfinamides by Double-Inversion Nucleophilic Displacement.



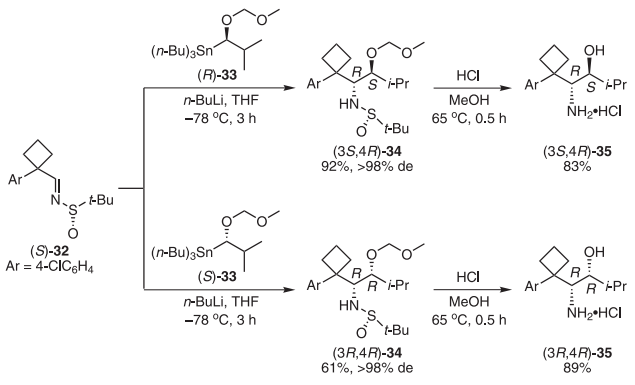

*Ref. 28*

**eq 2**



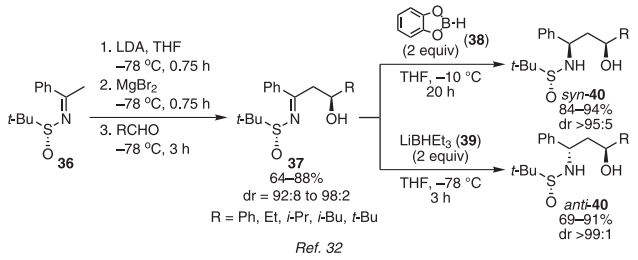

*Ref. 29*

**Scheme 8**. Chiral Sulfinyl Auxiliaries in the Asymmetric Synthesis of $C_2$-Symmetrical Vicinal Diamines.

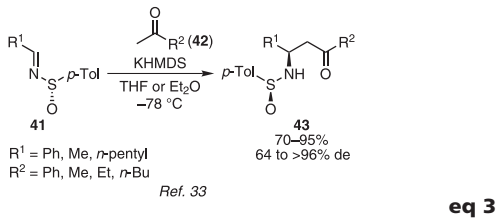



*Ref. 31*

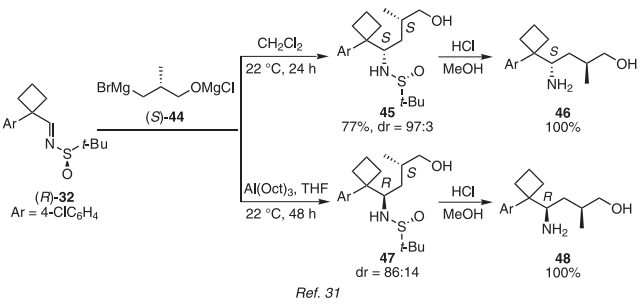
**Scheme 9**. Asymmetric Synthesis of *syn*- and *anti*-1,2-Amino Alcohols.



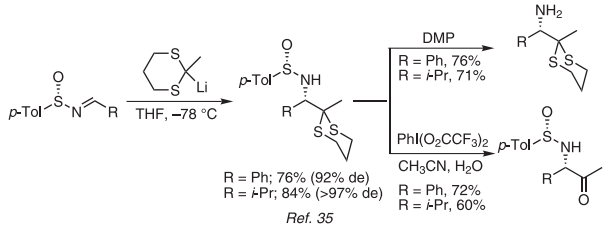

**Scheme 10**. Ellman's Asymmetric Synthesis of *syn*- and *anti*-1,3-Amino Alcohols.



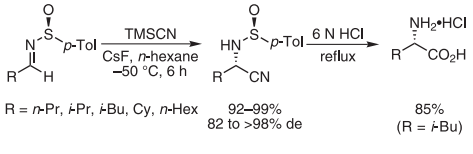

**eq 3**




**Scheme 11**. Asymmetric Synthesis of 1,4-Amino Alcohols.




**Scheme 12**. Asymmetric Synthesis of α-Amino Ketones.




**Scheme 13**. Asymmetric Synthesis of α-Amino Acids.

N–H insertion led to cis 3-oxopyrrolidinephosphonates in 62–98% de's. Removal of the 3-oxo group led to cis, 5-substituted pyrrolidinephosphonates.

The same group also developed an alternative approach for preparing five-, six-, and seven-membered cyclic α-amino phosphonates, in enantiomerically pure form, via the highly diastereoselective addition of metal phosphonates to masked oxosulfinyl imines. Hydrolysis of the resulting masked oxo-α-amino phosphonates, followed by reduction of the intermediate cyclic imino phosphonates, afforded the cyclic α-amino phosphonates in good overall yields.[41]

### 3.7. Synthesis of α-Amino Organostannanes

Chiral, nonracemic α-amino organostannanes have been prepared by the highly diastereoselective (de > 98%) addition of $Bu_3SnLi$ to chiral *tert*-butanesulfinyl imines (**Scheme 15**).[42] The resulting adducts were obtained in excellent yields, and were readily converted to enantiomerically enriched *N*-Boc-protected α-amino organostannanes with complete retention of configuration. Kells and Chong also extended this method to the preparation of chiral α-sulfonamido organostannanes to be used in the Stille cross-coupling reaction.[43] Addition of lithium tributylstannane to (*R*)-*tert*-butanesulfinyl imines derived from aryl aldehydes provided α-sulfinamidostannanes with high diastereoselectivities (de > 98%). Subsequent oxidation with *m*-CPBA gave α-sulfonamidostannanes, which were subjected to Pd/Cu-catalyzed Stille-type coupling with benzoyl chloride. Best yields were achieved using the electron-rich tris(2,4,6-trimethoxyphenyl)phosphine as the ligand. Inversion of configuration at the benzylic carbon was observed.[43]

## 4. Chiral Sulfoxides and Sulfinamides as Ligands in Catalytic Asymmetric Reactions

Chiral sulfoxides and sulfinamides constitute a valuable class of chiral ligands, where chirality resides at sulfur rather than carbon, and where coordination to the metal can occur through nitrogen, sulfur, or oxygen.

### 4.1. Chiral Sulfoxide-Based Ligands

Chiral sulfoxides have been used in a number of transition-metal-catalyzed asymmetric carbon–carbon-bond-forming reactions and enantioselective protonation reactions.[44,45] For example, Hiroi and co-workers utilized new chiral oxazoline–sulfoxide ligands for the catalytic asymmetric Diels–Alder reaction of cyclopentadiene and *N*-acryloyloxazolidinone (**eq 6**).[46] These results revealed that the presence of a methoxy group in both the naphthylsulfinate substituent and the oxazoline group was crucial to achieving high asymmetric induction (entry 2). Chiral centers in the oxazoline group and at the sulfur atom play a critical role in the asymmetric Diels–Alder reaction, as removal of either one results in poor enantioselectivities.

*N*-Phosphanopyrrole and indole, substituted at the 2 position with a chiral sulfoxide group, have successfully been utilized by Hiroi's group as new ligands in the enantioselective palladium-catalyzed allylic alkylation reaction.[47]

### 4.2. Chiral Sulfinamide-Based Ligands

#### 4.2.1. Asymmetric Diels–Alder Reaction

By developing bis(sulfinyl)imidoamidine (SIAM) ligands, Ellman and coworkers made an outstanding contribution to the chiral Lewis acid catalyzed Diels–Alder reaction of cyclic and acyclic dienes with *N*-acryloyloxazolidinones (**eq 7**).[5f,48] Indeed, SIAM ligands proved far more powerful than previously developed sulfinyl-based ligands. For example, the Diels–Alder reaction of cyclopentadiene and *N*-acryloyloxazolidinone in the presence of

10 mol % $Cu(SbF_6)_2$ and 11 mol % **52** provided the cycloadduct in 96% yield, 98% de, and 98% ee. Modification of the substitution pattern in the SIAM ligand resulted in no further improvement in reactivity or selectivity. SIAM ligands derived from *tert*-butanesulfinamide and ketones provided inferior results. The substrate scope of this $Cu(SbF_6)_2$–SIAM catalytic system was investigated with ligand **52**. High selectivities were observed for imides derived from crotonic acid, cinnamic acid, and fumaric acid (entries 2–4). Less reactive dienes such as 1,3-cyclohexadiene led to the cycloadduct in only 50% yield and 90% ee.

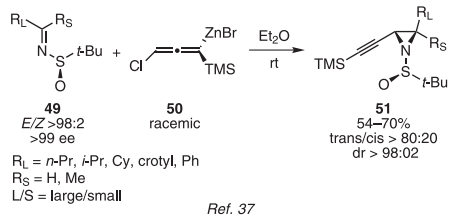
The Cu(II)–SIAM catalytic system proved more efficient than the usual bisoxazoline-based ligand system,[49] even for the more challenging Diels–Alder reaction with acyclic dienes (**eq 8**).[48] Indeed, the use of $Cu(SbF_6)_2$–SIAM catalysts led to high yields and excellent enantioselectivities for the cycloaddition of isoprene and 2,3-dimethylbutadiene. Incorporation of a substituent at the terminal position, or of a phenyl or ether group, in the dienes resulted in poor selectivities. Cycloaddition of 2,3-dimethylbutadiene with substituted dienophiles represented a more challenging set of substrates, and provided disappointing results with ligand **52**. However, using the more reactive *N*-(2,2,2-trifluoroethyl)-substituted SIAM analog of **52** resulted in the formation of the cycloadduct in 80% yield and 81% ee.

## 4.2.2. Asymmetric Allylic Alkylation

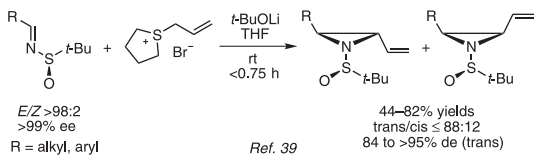
The usefulness of sulfinyl imine ligands in achieving excellent enantioselectivities in the palladium-catalyzed asymmetric allylation reaction has recently been reported by Ellman.[50] An initial optimization study was performed using phosphinooxazoline-based ligand **53a** in the asymmetric alkylation of 1,3-diphenylpropen-1-yl acetate with dimethyl malonate. It was determined that the Pd complex generated from ligand **53a** and a slight excess of $[Pd(allyl)Cl]_2$ (1:1.3) in methylene chloride gave optimal results with high conversion and 93% ee (**eq 9**). Modified ligands (**53b–e**) were prepared and studied in the reaction. Interestingly, using the *p*-toluenesulfinyl ligand **53b** led to poor conversion and no selectivity. Although ketimine ligand **53c** increased the rate of the reaction, a significant reduction in stereoselectivity was also observed. Replacement of phenyl substituents on the phosphorus atom in **53a** by cyclohexyl groups, as in **53d**, gave disappointing results as a longer reaction time was required and poor selectivity was obtained. Interestingly, the Pd complex derived from ligand **53e** was more active and selective and provided 96% ee with complete conversion in 2 hours. Additional experiments showed that ligand **53e** tolerated various ligand/Pd ratios and high-to-low concentrations. More importantly, a lower catalyst loading (5 mol %) provided complete conversion with a 95% isolated yield and 94% ee.

## 4.2.3. Asymmetric Hydrogenation of Olefins

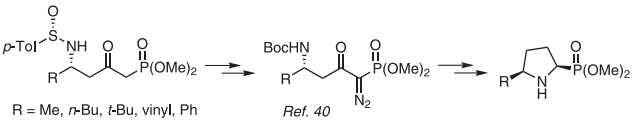
The value of these sulfinamide-based P,N ligands in the asymmetric hydrogenation of olefins has recently been demonstrated (**eq 10**).[51] Initial optimization focused on the hydrogenation of trisubstituted olefin **54a** using iridium complex **55**. The optimal reaction conditions consisted of treating **54a** with 5 mol % of **55** in dichloromethane under 25–100 bars of hydrogen gas pressure, and provided **56a** with >99% conversion and 94% ee. In order to explore the effect of catalyst structure on the turnover and enantioselectivity, an array of similar catalysts with modified sulfinamide moieties or phosphine substituents were prepared. Unfortunately, none was found as effective as **55**. Other functionalized olefins, e.g., **54b**, hydrogenated using catalyst **55**, provided **56b** with >99% conversion and 65% ee. A survey of other catalysts provided only disappointing results. Nonetheless, this work expands the scope of the P,N-sulfinyl imine



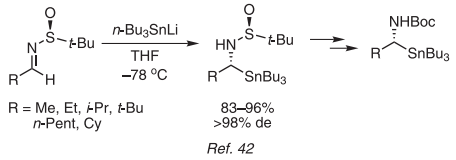

**eq 4**



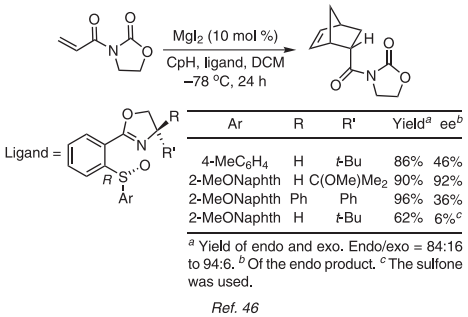

**eq 5**




**Scheme 14**. Asymmetric Synthesis of Cis 5-Substituted Pyrrolidine-2-phosphonates.



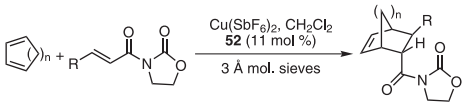

**Scheme 15**. Asymmetric Synthesis of α-Amino Organostannanes.

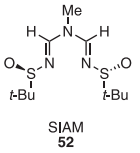



| Ar | R | R' | Yield[a] | ee[b] |
|---|---|---|---|---|
| 4-MeC$_6$H$_4$ | H | *t*-Bu | 86% | 46% |
| 2-MeONaphth | H | C(OMe)Me$_2$ | 90% | 92% |
| 2-MeONaphth | Ph | Ph | 96% | 36% |
| 2-MeONaphth | H | *t*-Bu | 62% | 6%[c] |

[a] Yield of endo and exo. Endo/exo = 84:16 to 94:6. [b] Of the endo product. [c] The sulfone was used.

**eq 6**



SIAM
**52**

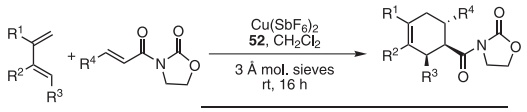
| n | R | T, °C | Time | Yield | dr | ee |
|---|---|---|---|---|---|---|
| 1 | H | –78 | 0.1 h | 96% | 99:1 | 98% |
| 1 | Me | –40 | 8 h | 76% | 98:2 | 97% |
| 1 | Ph | 0 | 16 h | 58% | 95:5 | 94% |
| 1 | $CO_2Et$ | –78 | 2 h | 85% | 97:3 | 96% |
| 1 | H[a] | –78 | 8 h | 95% | 99:1 | 98% |
| 2 | H | 0 | 16 h | 50% | 98:2 | 90% |

[a] **52** (1 mol %).

SIAM = bis(sulfinyl)imidoamidine

*Ref. 48*

**eq 7**

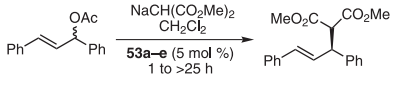


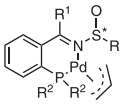

| $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield | ee |
|---|---|---|---|---|---|
| Me | H | H | H | 83% | 93% |
| Me[a] | Me | H | H | 96% | 92% |
| H[b] | H | Me | H | 18% | 41% |
| Ph[c] | H | H | H | 87% | 45% |
| $CH_2OTBDPS$ | H | H | H | 33% | 62% |
| Me | Me | H | $CO_2Et$ | <65% | 53% |

[a] 0 °C. [b] dr of product = 2.0:1.0:0.4; % ee is of major isomer. [c] 2 h.

*Ref. 48*

**eq 8**



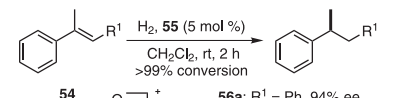
**L–Pd**
**53**

| Cat.[a] | R | $R^1$ | $R^2$ | ee |
|---|---|---|---|---|
| **53a** | *t*-Bu | H | Ph | 93% |
| **53b** | *p*-Tol | H | Ph | 0% |
| **53c** | *t*-Bu | Me | Ph | 56% |
| **53d** | *t*-Bu | H | Cy | 49% |
| **53e** | *t*-Bu | H | *o*-Tol | 96% |
| **53e**[b] | *t*-Bu | H | *o*-Tol | 96% |
| **53e**[c] | *t*-Bu | H | *o*-Tol | 94% |

[a] **L** (30 mol %),**L–Pd** 1:1.3.
[b] **L–Pd** 1:1.
[c] **L** (5 mol %),**L–Pd** 1:1.

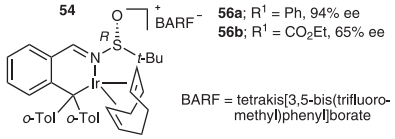
*Ref. 50*

**eq 9**




**54**

**56a**; $R^1$ = Ph, 94% ee
**56b**; $R^1$ = $CO_2Et$, 65% ee



BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

**55**

*Ref. 51*

**eq 10**

based catalyst to challenging unfunctionalized olefin substrates and to obtaining valuable structure–activity relationships for sulfinyl imine based ligands in the iridium-catalyzed asymmetric hydrogenation of olefins.

## 5. Application to the Asymmetric Synthesis of Biologically Active Targets

### 5.1. Synthesis of SC-53116

SC-53116 is a drug candidate for serotonin 5-$HT_4$ agonist. Its recent, efficient, and elegant asymmetric synthesis began with the self-condensation of a metalloenamine (derived from *tert*-butylsulfinamide and LiHMDS) in the presence of DMPU in THF, and led to the desired self-condensation product in 55% yield and a good diastereomeric ratio. This compound underwent a novel and selective microwave-assisted decomposition of the *N*-sulfinyl imine moiety to give the corresponding nitrile in 84% yield (**Scheme 16**).[52] Elaboration of the nitrile provided SC-53116 in 29% overall yield (5 steps), a significant improvement over the previously reported synthesis.

### 5.2. Total Synthesis of (6R,7S)-7-Amino-7,8-dihydro-α-bisabolene

(6*R*,7*S*)-7-Amino-7,8-dihydro-α-bisabolene is an antimicrobial metabolite**.** Its first asymmetric total synthesis utilized a single chiral sulfinyl imine to control the formation of two adjacent stereocenters (**Scheme 17**).[53] The key step, allylation of amidine **57**, was performed at –78 °C with allyl bromide in the presence of KHMDS to provide **58** in 82% yield as a single diastereomer. *N*-Sulfinylamidine **57** was used, because of the increased nucleophilicity of the corresponding metalloenamine towards alkyl halides, as compared to that of metalloenamines derived from *N*-sulfinyl ketimines. The desired ketimine **59** was prepared in 82% yield using a $CeCl_3$-mediated addition of MeLi to amidine **58**. Subsequent ring-closing metathesis of **59** proceeded in 87% yield using a Grubbs second-generation catalyst. This organometallic addition to *N*-sulfinyl ketimines provides the only general method to date for the asymmetric synthesis of tertiary carbinamines. Finally, precomplexation of imine **60** with $Me_3Al$ at –78 °C, followed by addition of 4-methyl-3-penten-1-yllithium and deprotection with HCl in MeOH, led to the natural product, **61**, in 49% yield as a single diastereoisomer.

### 5.3. Asymmetric Synthesis of (–)-Pateamine

(–)-Pateamine (**65**), a unique thiazole-containing 19-membered bislactone that is isolated from a marine sponge, exhibits potent immunosuppressant activity. Its synthesis has been described by Remuiñán and Pattenden, and involves the asymmetric addition of a functionalized enolate, derived from **62**, to *N*-sulfinyl imine **63** (**Scheme 18**).[54] The resulting β-amino ester, **64**, was isolated in 63% yield and 85% diastereomeric excess. Further synthetic manipulations led to the natural product. Davis and co-workers have also employed this approach in concise and convergent asymmetric syntheses of other biologically active compounds.[55]

### 5.4. Synthesis of Polyoxamic Acid Lactone

The sulfinyl imine based asymmetric Strecker reaction represents one of the most efficient and practical methods for the synthesis of optically active α-amino acids. Polyoxamic acid, the key structural unit in the natural product polyoxin J, was recently synthesized in an asymmetric fashion starting with the addition of $Et_2AlCN$ to a functionalized *p*-toluenesulfinyl imine. Subsequent deprotection and cyclization of the α-(sulfinylamino)nitrile led to polyoxamic acid lactone (**Scheme 19**).[55]

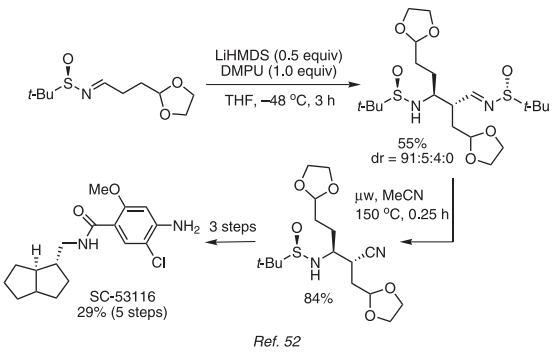
### 5.5. Synthesis of Single Enantiomers of Sibutramine and Cetirizine

The first application of tunable alkyl or aryl sulfinamides was recently reported for the asymmetric synthesis of **67**, a key intermediate of enantiopure sibutramine. The racemic form of sibutramine is currently used for the treatment of obesity. Among the variety of sulfinamides examined, *tert*-butanesulfinamide and (triethyl)methanesulfinamide (TESA) provided the best yields and selectivities for this process. After further optimization with respect to temperature, additives, and solvent, it was determined that using THF as the solvent at –78 °C with $BF_3$•$OEt_2$ as an additive gave (*R*)-**67** in excellent yield and >99% optical purity. Using (*R*)-(triethyl)methanesulfinyl imine gave excellent selectivity and, unlike the (*R*)-*tert*-butanesulfinyl imine derivative, did not generate any undesirable odor during the acid-mediated deprotection. A chromatography-free process was demonstrated in a single vessel using commercially available **66** as a starting material (**Scheme 20**).[56] Thus, treatment of nitrile **66** with Red-Al® in toluene followed by condensation with (*R*)-TESA gave the desired sulfinyl imine. Diastereoselective addition of *i*-BuLi in the presence of $BF_3$•$OEt_2$ at –78 °C, followed by cleavage of the chiral auxiliary, afforded (*R*)-**67** in 99% enantiomeric excess. (*R*)-**67** was isolated as the D-tartrate salt in 83% overall yield, >99% enantiomeric excess, and >99.5% chemical purity.

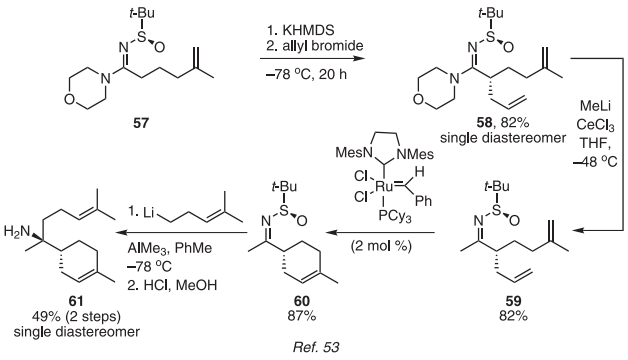
(*S*)-Cetirizine dihydrochloride is a nonsedating histamine H1-receptor antagonist used for the treatment of allergy and is currently marketed as Xyzal® in Europe. Senanayake and co-workers reported an effective asymmetric synthesis of the enantiopure key intermediate, **68**. Addition of PhMgBr to *N*-*tert*-butanesulfinyl-*p*-chlorobenzaldimine in toluene gave **68** as the major enantiomer with moderate enantiopurity (75% ee).[57] The yield and selectivity were later improved by careful tuning of the sulfinamide. Indeed, using 2,4,6-triisopropylphenylsulfinamide, **68** was obtained in 91% ee at 0 °C and 94% ee at –20 °C (**eq 11**).[58]

## 6. Conclusions

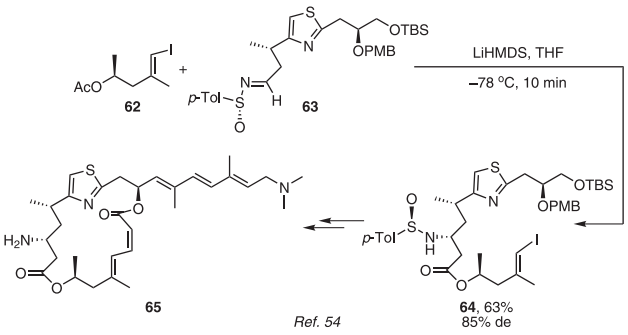
The scope of applications of chiral sulfinamides and chiral sulfoxides has grown substantially in the past five years. Furthermore, the utilization of chiral ligands based on sulfinyl imines and sulfoxides is growing at a rapid rate. However, the stereoselective synthesis of such important chiral auxiliaries has been limited to a few approaches, such as the asymmetric oxidation of prochiral sulfides and disulfides, or the use of chiral sulfinyl transfer agents. Recent progress in the general and modular synthesis of chiral sulfinamides and chiral sulfoxides using activated 1,2,3-oxathiazolidinone-2-oxides provides easy access to many structurally diverse sulfinamides and sulfoxides. Chiral sulfinamides have proven highly efficient as chiral auxiliaries in the synthesis of a variety of optically active amines, including diamines, amino alcohols, aziridines, and amino phosphonates. Structurally diverse sulfinamides are a powerful optimization tool and lead to improved yields and enhanced selectivities. In addition, chiral sulfinamides and chiral sulfoxides have been widely utilized as ligands in catalytic asymmetric processes, such as the Diels–Alder and the allylic alkylation reactions. A number of these newly developed methodologies have been successfully applied to the asymmetric synthesis of biologically active compounds and drug candidates. We anticipate that the use of this array of sulfinamides and sulfoxides will increase as these reagents become readily available. These new developments may be applied efficiently in economical and safe processes for the large-scale production of complex biologically important targets.



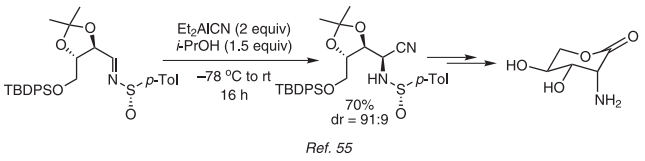

**Scheme 16**. Synthesis of SC-53116.



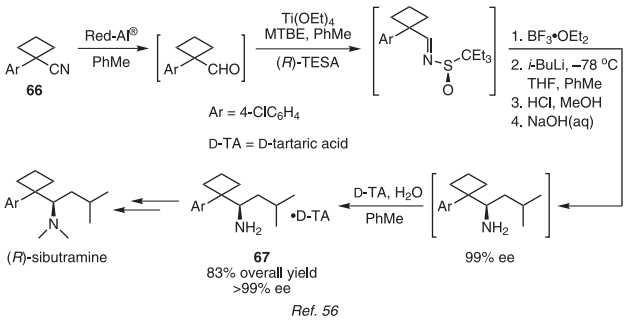

**Scheme 17**. Ellman's Asymmetric Synthesis of (6*R*,7*S*)-7-Amino-7,8-dihydro-α-bisabolene.



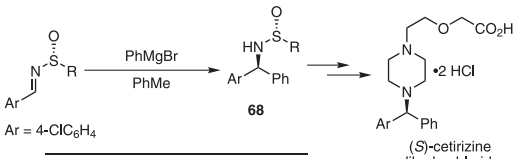

**Scheme 18**. Asymmetric Synthesis of (–)-Pateamine.




**Scheme 19**. Synthesis of Polyoxamic Acid Lactone.




**Scheme 20**. Asymmetric Synthesis of Sibutramine Precursor.




| R | T, °C | Yield of **68** | ee of **68** |
|---|---|---|---|
| *t*-Bu | 0 | 81% | 75% |
| 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$ | 0 | 84% | 91% |
| *t*-Bu | –20 | 83% | 82% |
| 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$ | –20 | 80% | 94% |

*Ref. 57,58*

**eq 11**

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**Chris H. Senanayake** was born in Sri Lanka and received his B.S. degree (First Class) there. He completed the requirements for his M.S. degree in synthetic chemistry with Professor Thomas Kinstle at Bowling Green State University. He obtained his Ph.D. degree in 1987 under the guidance of Professor James H. Rigby at Wayne State University, where he worked on the total synthesis of complex natural products, such as ophiobolanes, and completed the first total synthesis of grosshemin in the guaianolide family. He then undertook a postdoctoral fellowship with Professor Carl R. Johnson to work on the total synthesis of polyol systems, such as amphotericin B and compactin analogs, and the synthesis of C-nucleoside precursors.

In 1989, he joined The Dow Chemical Co. as a senior research chemist in the Department of Process Development, and, in 1990, accepted a position with the Merck Process Research Group as a senior research chemist. After a series of accomplishments in synthetic organic chemistry and receiving a prestigious Merck Management Award in chemistry, he was promoted to Research Fellow in 1993. In 1996, he joined Sepracor, Inc., as Director of Chemical Process Research. He was promoted to Senior Director of Chemical Process Research in 1998, and Executive Director of Chemical Process Research in 2001. He was responsible for the design and development of economical chemical processes for the commercialization of pharmaceutical drugs. In 2002, he joined Boehringer Ingelheim Pharmaceuticals, Inc., as Director of Chemical Process Research, and, in 2003, was named Director, Chemical Development. He currently leads a group of company scientists located in Ridgefield, CT, and Richmond, VA.

Dr. Senanayake's research interests focus on the development of new asymmetric methods for the synthesis of bioactive molecules and heterocycles and on catalytic, enzymatic, and mechanistic studies. He has published and lectured in the area of practical asymmetric synthesis and many disciplines of organic chemistry on how to develop drugs practically and economically in large-scale operations. He is the author of about 125 papers and patents on the design and synthesis of improved chemical entities. Dr. Senanayake is a member of the Editorial Advisory Board of *Organic Process Research & Development*.

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aldol reactions, Diels–Alder, and hetero-Diels–Alder reactions. After a brief postdoctoral stint with Professor G. E. Keck, he joined the process research group at Bristol-Myers Squibb as a Research Investigator I. He was promoted to Research Investigator II in 1998 for his accomplishments in the antiviral and oncology programs. In 1999, he joined the process research group at Sepracor, Inc., in Marlboro, MA, as a principal research scientist. At Sepracor, he and his group contributed to a number of fast-track projects and, in 2002, was named Associate Research Fellow. In late 2002, he joined Boehringer Ingelheim in Ridgefied, CT, where he is currently Associate Director for Process Research. His research interests include catalytic asymmetric synthesis and the development of practical processes for the large-scale production of biologically active compounds. He is the author of more than 30 papers and patents.

**Zhi-Hui Lu** was born in China in 1966. He received his B.S. degree from Peking University (1988) and his Ph.D. (1994) from the Shanghai Institute of Organic Chemistry (with Professor W. S. Zhou) and the University of Geneva, Switzerland (with Professor C. W. Jefford). He spent one year with Professor H. C. Brown at Purdue University (1995) and one-and-a-half years with Professor J. A. Marshall at the University of Virginia as a postdoctoral researcher. In 1997, he joined DuPont-Merck Pharmaceuticals as a senior research scientist in the Department of Process Research and Development, where he contributed to the development of a scalable process for the asymmetric synthesis of DMP963. In 1999, he joined Sepracor as a senior research chemist. After a series of achievements, he was promoted to principal research chemist in 2001. Following a short stay with Enanta Pharmaceuticals, he joined Boehringer Ingelheim Pharmaceuticals as a group leader in late 2002, and was promoted to his current position of Senior Principal Scientist supervising the Process Research Group in Richmond, Virginia. His research interests include the development of new synthetic processes, organometallic chemistry, and asymmetric catalysis. He is the author of about 45 papers and patents.

**Zhengxu (Steve) Han** was born in China. He received his B.S degree (1984) and his Ph.D. (1989) in organic chemistry from Lanzhou University. After teaching in the Department of Chemistry of Lanzhou University for two years, he moved to Tübingen University, Germany, in 1991 as a fellow of the Alexander von Humboldt Foundation. From 1993 to 1995, he worked as a postdoctoral fellow at the University of California, Berkeley, and from 1995 to 1997 at the University of Tennessee in Knoxville. In 1998, he joined the process research group at Sepracor, Inc., and, in 2005, he accepted the position of principal scientist in the process research group at Boehringer Ingelheim. His research interests center on the development of new methods for the efficient asymmetric synthesis of pharmaceutical ingredients and intermediates and of chiral amines, on asymmetric C–C- and C–N-bond-forming reactions, and on catalysis chemistry.

**Isabelle Gallou** was born in 1974 in Paris, France. She received her "Diplôme d'Ingénieur" in chemistry and chemical engineering in 1999 from the École Supérieure de Chimie Physique Electronique de Lyon. She obtained her Ph.D. degree in 2002 under the guidance of Professor T. V. RajanBabu at The Ohio State University, where she worked on the development of selective palladium- and rhodium-catalyzed processes for the asymmetric synthesis of structurally relevant synthons. She then joined Boehringer Ingelheim under the direct supervision of Drs. Vittorio Farina and Chris Senanayake. Her research interests include catalysis and asymmetric reactions for C–C- and C–N-bond formation, as well as the development of practical processes for the large-scale production of active pharmaceutical ingredients and intermediates.

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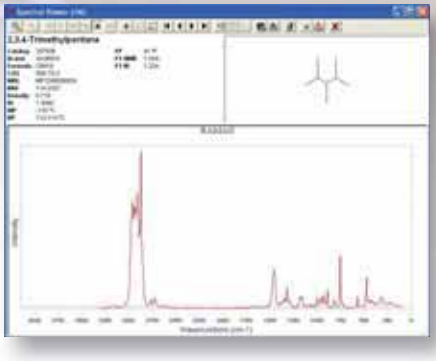

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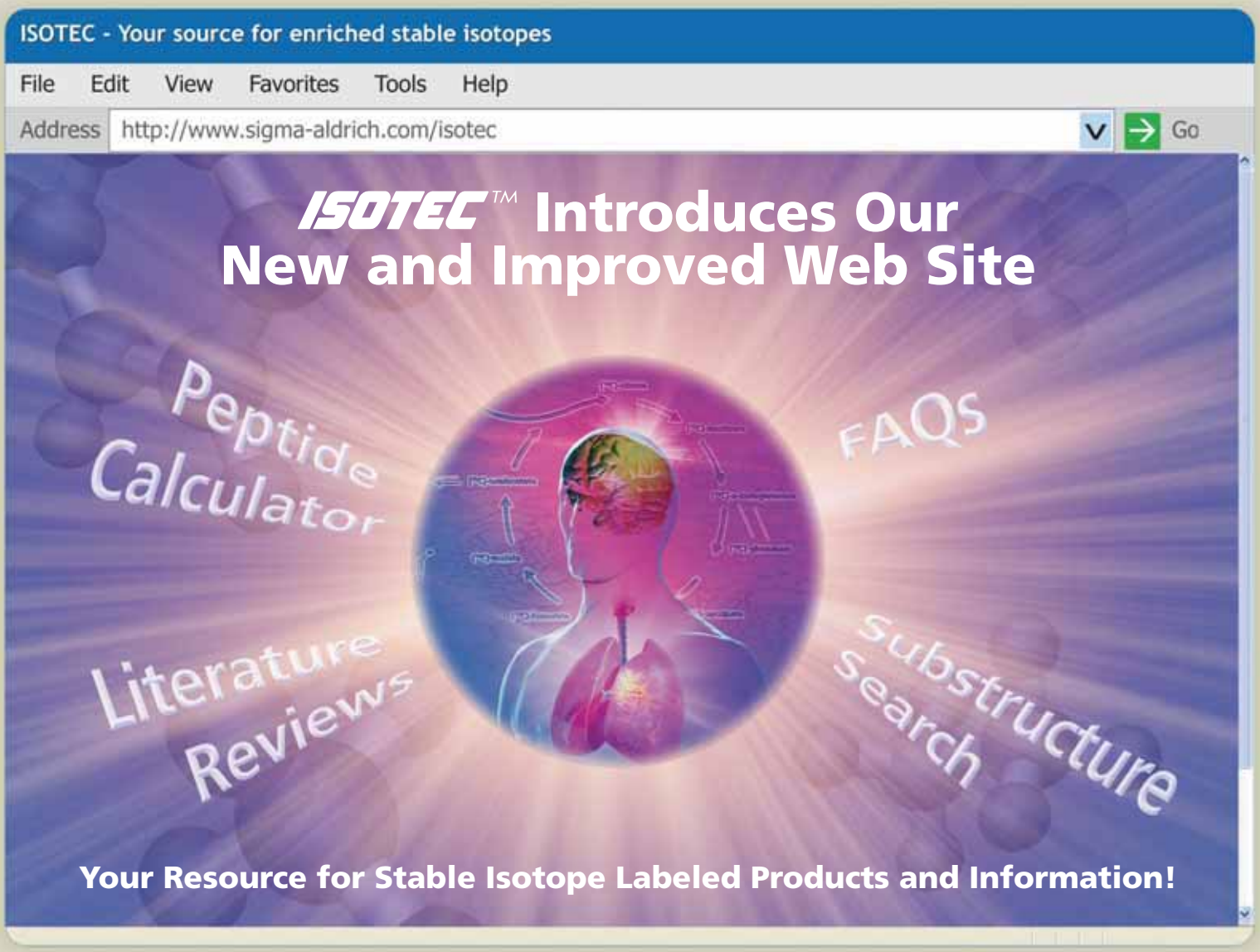


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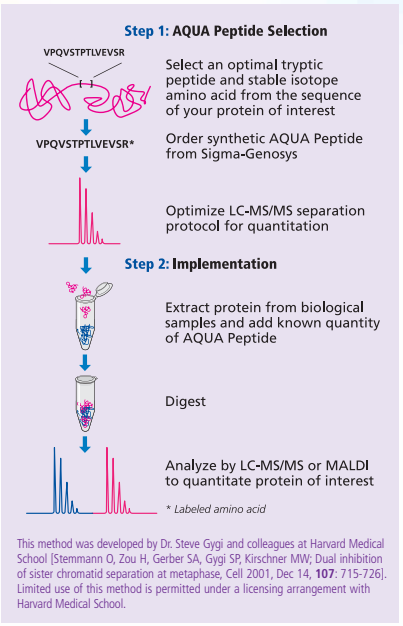
(1) Gerber, S. A.; Rush, J.; Stemman, O.; Kirschner, M. W.; Gygi, S. P. *Proc. Natl. Acad. Sci. U.S.A. (PNAS)* **2003**, *100*, 6940.




This method was developed by Dr. Steve Gygi and colleagues at Harvard Medical School [Stemmann O, Zou H, Gerber SA, Gygi SP, Kirschner MW; Dual inhibition of sister chromatid separation at metaphase, Cell 2001, Dec 14, **107**: 715-726]. Limited use of this method is permitted under a licensing arrangement with Harvard Medical School.

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| Description | Cat. No. |
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| IKA® lab dancer™ test tube shaker, 115 V | **Z560731-1EA** |
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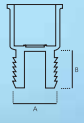
The Suba•Seal® name is well-known as the best-quality fold-over closure with serrated stopper. Sigma-Aldrich is now the exclusive worldwide source for genuine Suba•Seal® products. We have increased your choice of colors to give you more options to color-code your applications, and are offering a silicone rubber version for higher-temperature use. Check out the product table below for more information that will help you choose the best Suba•Seal® closure for your application.

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

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



| Suba•Seal® No. | Fits Neck I.D. (mm) | Length (mm) A | Length (mm) B | Use with | *White Rubber* Cat. No. | *Red Rubber* Cat. No. |
|---|---|---|---|---|---|---|
| 13 | 9.5 | 9.6 | 9.3 | ⅎ10/30 joints | **Z167258** | **Z124567** |
| 25 | 14.0 | 14.1 | 12.5 | ⅎ14/20 joints | **Z167282** | **Z124591** |
| 33 | 17.5 | 18.0 | 12.7 | Sure/Seal™ bottles | **Z167290** | **Z124613** |
| 37 | 19.0 | 20.4 | 15.7 | ⅎ19/22 joints | **Z167304** | **Z124621** |
| 45 | 22.0 | 23.0 | 20.4 | ⅎ24/40 joints | **Z167320** | **Z124656** |
| 57 | 27.0 | 28.3 | 20.5 | ⅎ29/42 joints | **Z167355** | **Z124680** |

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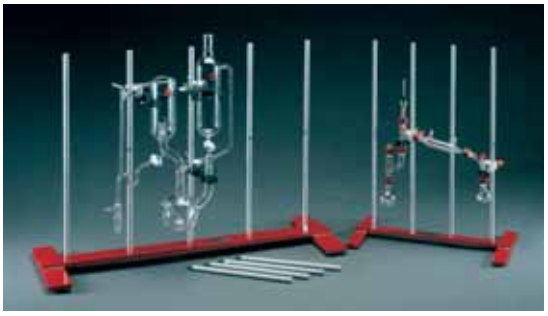
# Aldrich® Benchrack™

## *Portable Lattice Systems*

These sturdy systems fit easily on a benchtop or in a fume hood, and may be disassembled for storage or transport. A Benchrack™ has a durable, red powder–epoxy enamel coated, heavy-gauge steel base with nonslip rubber feet. Solid, 11¾-in. long, aluminum lattice rod sections screw into each other for variable height configurations. Accessory lattice rod sections are available for increasing height and for horizontal stabilization in heavy-duty applications. Entire system assembles without tools. For permanent setups, machined flats on lattice rod sections may be tightened with a wrench.

The mini-size Benchrack™ is ideal for use with microscale glassware and as a support in medium- and large-size Aldrich AtmosBags™.



| Description | Cat. No. |
|---|---|
| Mini size, 4 positions, 8 rods<br>Includes base and ½-in. diam lattice rod sections.<br>Base size: 19 in. × 8 in. | **Z225657-1EA** |
| Standard size, 4 positions, 8 rods<br>Includes base and ⅝-in. diam lattice rod sections.<br>Base size: 27⅝ in. × 12 in. | **Z225630-1EA** |
| Standard size, 5 positions, 10 rods<br>Includes base and ⅝-in. diam lattice rod sections.<br>Base size: 35 in. × 12 in. | **Z225649-1EA** |
| NEW V-Shaped, 7 positions, 14 rods<br>Includes V-shaped base and ⅝-in. diam lattice rod sections.<br>Base size: 48 in. | **Z560138-1EA** |

## NEW *Large-Lattice-System Kits*

The red powder–epoxy enamel coated, heavy-gauge frames of the Benchrack™ floor-mounted and wall-mounted lattice systems bolt together and are expandable using the add-on parts listed below each system. These systems have 3 vertical and 3 horizontal ½-in. diam. aluminum lattice rods that adjust to any position. The kit includes 6 machined aluminum rod supports and 9 rod clamps with stainless steel set screws and Allen wrench.

To secure lattice systems to the floor or wall, order mounting clamp set Z560200-4EA separately.

| Description | Cat. No. |
|---|---|
| Floor-Mounted lattice system<br>Size: 72 in. H × 50 in. W | **Z560154-1EA** |
| Wall-Mounted lattice system<br>Size: 32 in. H × 26 in. W | **Z560219-1EA** |
| Mounting clamp set | **Z560200-4EA** |

Add-On parts available separately, see **sigma-aldrich.com/labequipment**.



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# Aldrich® Ver*SA*Funnel™

## Buchner Funnels with Modular Components

Interchangeable and replaceable components permit the use of a wide range of funnel porosities and capacities at minimal expense. It is no longer necessary to replace an entire Buchner funnel because of a clogged filter frit, or broken rim or stem.

## Features

- Five interchangeable frit porosities: 4 microns up to 175 microns
- PTFE cup gasket seals edge of frit during use
- Replaceable components: frits, gaskets, funnel tops, bottoms, and connectors

## Getting Started with Ver*SA*Funnel™ Is Simple

1. Order complete Ver*SA*Funnel™ assemblies below. Assembly includes funnel top, bottom, filter disc, PTFE gasket, and threaded HDPE connector.
2. Order spare components in the tables that follow.

## Complete Ver*SA*Funnel™ Assemblies

| Cap. (mL) | Porosity (µm) | Disc Diam (mm) | Cat. No. |
|---|---|---|---|
| 30 | 4–8 | 24 | **Z554251-1EA** |
| | 10–20 | 24 | **Z554278-1EA** |
| | 25–50 | 24 | **Z554286-1EA** |
| | 70–100 | 24 | **Z554294-1EA** |
| | 145–175 | 24 | **Z554308-1EA** |
| 60 | 4–8 | 24 | **Z554316-1EA** |
| | 10–20 | 24 | **Z554324-1EA** |
| | 25–50 | 24 | **Z554332-1EA** |
| | 70–100 | 24 | **Z554340-1EA** |
| | 145–175 | 24 | **Z554359-1EA** |
| 140 | 4–8 | 50 | **Z554367-1EA** |
| | 10–20 | 50 | **Z554375-1EA** |
| | 25–50 | 50 | **Z554383-1EA** |
| | 70–100 | 50 | **Z554391-1EA** |
| | 145–175 | 50 | **Z554405-1EA** |
| 350 | 4–8 | 50 | **Z554413-1EA** |
| | 10–20 | 50 | **Z554421-1EA** |
| | 25–50 | 50 | **Z554448-1EA** |
| | 70–100 | 50 | **Z554456-1EA** |
| | 145–175 | 50 | **Z554464-1EA** |
| 600 | 10–20 | 90 | **Z554472-1EA** |
| | 25–50 | 90 | **Z554480-1EA** |
| | 70–100 | 90 | **Z554499-1EA** |
| | 145–175 | 90 | **Z554502-1EA** |
| 1,500 | 10–20 | 90 | **Z554510-1EA** |
| | 25–50 | 90 | **Z554529-1EA** |
| | 70–100 | 90 | **Z554537-1EA** |
| | 145–175 | 90 | **Z554545-1EA** |



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## Spare Filter Frits

Frits of different porosities but of the same diameter are interchangeable. Order PTFE cup gaskets separately below.

| Disc Diam (mm) | Porosity (µm) | Cat. No. |
|---|---|---|
| 24 | 4–8 | **Z555010-1EA** |
| | 10–20 | **Z555029-1EA** |
| | 25–50 | **Z555037-1EA** |
| | 70–100 | **Z555045-1EA** |
| | 145–175 | **Z555053-1EA** |
| 50 | 4–8 | **Z555061-1EA** |
| | 10–20 | **Z555088-1EA** |
| | 25–50 | **Z555096-1EA** |
| | 70–100 | **Z555118-1EA** |
| | 145–175 | **Z555126-1EA** |
| 90 | 10–20 | **Z555134-1EA** |
| | 25–50 | **Z555142-1EA** |
| | 70–100 | **Z555150-1EA** |
| | 145–175 | **Z555169-1EA** |

## Replacement PTFE Cup Gaskets

| Disc Diam (mm) | Cat. No. |
|---|---|
| 24 | **Z554987-1PAK** |
| 50 | **Z554995-1PAK** |
| 90 | **Z555002-1PAK** |

## Replacement Ver*SA*Funnel™ Tops, Bottoms, and Connectors

| Description | Funnel Cap. (mL) | Cat. No. |
|---|---|---|
| Funnel top | 30 and 60 | **Z554863-1EA** |
| Funnel top | 140 and 350 | **Z554871-1EA** |
| Funnel top | 600 and 1500 | **Z554898-1EA** |
| Funnel bottom | 30 and 60 | **Z554901-1EA** |
| Funnel bottom | 140 and 350 | **Z554936-1EA** |
| Funnel bottom | 600 and 1500 | **Z554944-1EA** |
| Connector, HDPE | 30 and 60 | **Z554952-1EA** |
| Connector, HDPE | 140 and 350 | **Z554960-1EA** |
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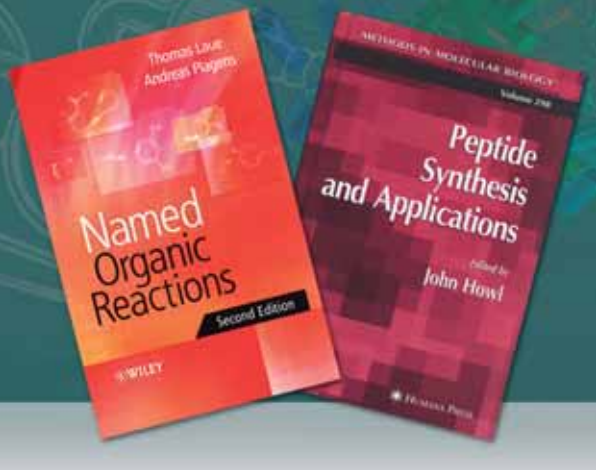


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## CHEMICAL SYNTHESIS TITLES

### Solid-Phase Organic Synthesis

*K. Burgess, Wiley, 1999, 296pp. Hardcover.* This work brings together the latest research in the field, highlighting and reviewing some of the hottest topics relevant to combinatorial chemistry, including solid-phase synthesis of natural product derivatives, synthesis of guanidine, palladium catalyzed C–C-bond-forming reactions, resin-supported capture agents and other reagents, synthesis on pins, and monitoring of supported reactions using IR.

**Z421731**

### 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 use the reagents, and provides key reactions to demonstrate where the 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**

### Named Organic Reactions, Second Edition

*T. Laue and A. Plagens, Wiley, 2005, 320pp. Softcover.* This second edition contains concise information on 134 carefully chosen named organic reactions—the standard set for synthetic organic chemistry courses. Each reaction is detailed with clearly drawn mechanisms, references from the primary literature, well-written accounts covering the mechanical aspects of the reactions, and the details of side reactions and substrate limitations. For the second edition, the complete text has been revised and updated, and five new reactions have been added: the Baylis–Hillmann, Sonogashira, and Pummerer reactions, and the Swern oxidation and cyclopropanation.

**Z703745**

### Principles and Applications of Asymmetric Synthesis

*G.-Q. Lin, Y.-M. Li, and A. S. C. Chan, Wiley, 2001, 536pp. Hardcover.* This covers more than 450 reactions, including important stoichiometric and catalytic asymmetric reactions. The first chapter reviews the basic principles, common nomenclature, and analytical methods, while the remainder of the book is organized according to reaction type. The text examines such topics as: C–C- and C–O-bond formations, asymmetric synthesis using the Diels–Alder reaction and other cyclizations, applications to the total synthesis of natural products, and the use of enzymes.

**Z511811**

### Peptide Synthesis and Applications

*J. Howl, Ed., Humana Press, 2005, 272pp. Hardcover.* Experts describe in detail the methodologies of contemporary peptide synthesis and illustrate their numerous applications. Techniques presented include protocols for chemical ligation, the synthesis of cyclic and phosphotyrosine-containing peptides, lipoamino acid and sugar-conjugated peptides, and peptide purification and analysis. Additional chapters detail methodologies and instrumentation for high-throughput peptide synthesis, many different applications of peptides as novel research tools and biological probes, and the design and application of fluorescent-substrate-based peptides that can be used to determine the selectivity and activity of peptidases. A practical guide to the identification of proteins using mass spectrometric analyses of peptide mixtures is also included.

**Z703826**

### Handbook of Organopalladium Chemistry for Organic Synthesis, 2-Volume Set

*E. Negishi and A. de Meijere, Eds., Wiley, 2002, 3424pp. Hardcover.* 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. This is the first comprehensive and authoritative handbook on organopalladium reagents and catalysts. Editor Ei-ichi Negishi assembles contributions from several dozen international authorities on the use of palladium reagents and catalysts. The contents are organized by reaction type, making the two-volume set of maximum utility to the bench synthetic chemist.

**Z513865**

## DRUG DISCOVERY TITLE

### High Throughput Analysis for Early Drug Discovery

*J. Kyranos, Ed., Elsevier, 2004, 350pp. Hardcover.* This book offers concise and unbiased presentations by synthetic and analytical chemists, who have been involved in creating and moving the field of combinatorial chemistry into the academic and industrial mainstream. Each chapter or section begins with a description of the synthesis approach and its advantages. The description of various combinatorial and high-throughput parallel synthesis techniques provides a relevant point of entry for synthetic chemists, who need to set up appropriate characterization methods for their organizations.

**Z703958**

## MATERIALS SCIENCE TITLES

### The Chemistry of Nanomaterials: Synthesis, Properties and Applications, 2-Volume Set

*C. N. R. Rao, A. Mueller, and A. K. Cheetham, Wiley-VCH, 2004, 761pp. Hardcover.* The authors cover the whole spectrum of nanomaterials, ranging from theory, synthesis, properties, to characterization and application, including such new developments as: quantum dots, nanoparticles, nanoporous materials, as well as nanowires, nanotubes, and nanostructural polymers; nanocatalysis, nanolithography, and nanomanipulation; and methods for the synthesis of nanoparticles.

**Z703850**

### Nanophysics and Nanotechnology: An Introduction to Modern Concepts in Nanoscience

*E. L. Wolf, Wiley, 2004, 187pp. Softcover.* Provides the first self-contained introduction to the physical concepts, techniques, and applications of nanotechnology, which should be of interest to readers grounded in college chemistry and physics. It is suitable for anyone in engineering, science, and materials science and to research workers of varied backgrounds in the interdisciplinary areas that make up nanotechnology. The author covers the latest examples of nanoscale systems, quantum concepts and effects, self-assembled nanosystems, manufacturing, and scanning probe methods of observation and fabrication, and single-electron and molecular electronics. He concludes with a look at the long-term outcomes.

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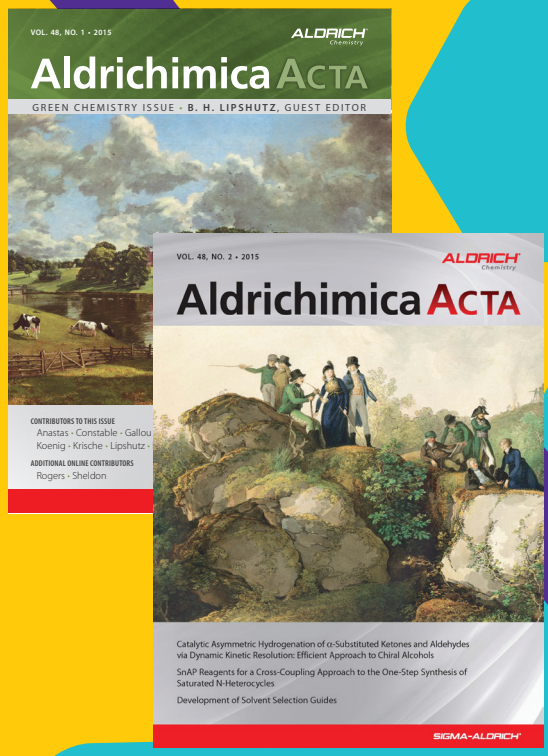


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