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# Aldrichimica ACTA

VOL. 36, NO. 3 • 2003
*(Last issue in 2003)*

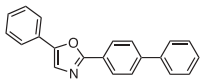
## Organosilicon Reagents: Synthesis and Application to Palladium-Catalyzed Cross-Coupling Reactions

## Cross Metathesis of Nitrogen-Containing Systems

# New Products from Aldrich R&D

## 2-(4-Biphenylyl)-5-phenyloxazole, 98%

**21,698-4** — 1g, 5g

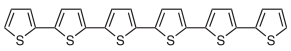


Widely used as an activator in $C_6F_6$-based scintillators for the study of α-particles,[1] γ-rays,[2] and solar neutrinos from β-decay.[3]

(1) Britvich, G.I. et al. *Nucl. Instrum. Methods Phys. Res., Sect. A* **1993**, *A326*, 483; *Chem. Abstr.* **1993**, *118*, 200826r. (2) Barabanov, I.R. et al. *Prib. Tekh. Eksp.* **1995**, 75; *Chem. Abstr.* **1995**, *123*, 125307v. (3) Barabanov, I.R. et al. *ibid.* **1996**, 41; *Chem. Abstr.* **1996**, *125*, 98054t.

## α-Sexithiophene

**59,468-7** — 1g

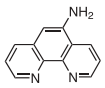


This thiophene oligomer is known for its semiconducting, electrochemical, and photoelectric properties.

Bungs, M.; Tributsch, H. *J. Appl. Electrochem.* **2002**, *32*, 91.

## 1,10-Phenanthrolin-5-ylamine, 97%

**63,150-7** — 5g

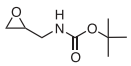


Employed in the formation of luminophores and metal–ligand complexes for the detection of chemical and biochemical materials.[1,2]

(1) Lecomte, J.-P. et al. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 3261. (2) Meggers, E. et al. *Helv. Chim. Acta* **1997**, *80*, 640.

## *tert*-Butyl *N*-(2-oxiranylmethyl)carbamate

**63,066-7** — 1g

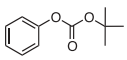


This functionalized epoxide can undergo hydrolytic kinetic resolution.[1] It has also been used as a building block for the construction of HIV proteinase inhibitors.[2,3]

(1) Schaus, S.E. et al. *J. Am. Chem. Soc.* **2002**, *124*, 1307. (2) Rocheblave, L. et al. *J. Med. Chem.* **2002**, *45*, 3321. (3) Kitchin, J. et al. *J. Med. Chem.* **1994**, *37*, 3707.

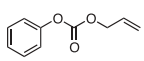
## *tert*-Butyl phenyl carbonate, 98%

**12,430-3** — 25g, 100g



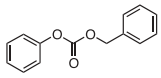
## Allyl phenyl carbonate, 97%

**63,065-9** — 1g, 5g



## Benzyl phenyl carbonate, 97%

**63,064-0** — 5g



These carbonates provide a practical and versatile method for selective Boc, Alloc, and Cbz protection of primary amines in simple symmetrical aliphatic diamines, and can selectively protect primary amines in the presence of secondary amines.

Pittelkow, M. et al. *Synthesis* **2002**, 2195.

## 2,4,6-Trichloropyridine, 97%

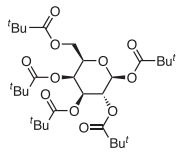
**63,353-4** — 1g, 5g

Building block for a variety of biologically active compounds such as some cephalosporins,[1] anticancer agents,[2] and herbicides.[3]

(1) D'Andrea, S.V. et al. *Tetrahedron* **2000**, *56*, 5687. (2) Kyoji, T. et al. Int. Patent Appl. WO 9534,559, Dec 21, 1995; *Chem. Abstr.* **1996**, *124*, 289559a. (3) Hisashi, K. et al. Eur. Patent Appl. EP 693,490, Jan 24, 1996; *Chem. Abstr.* **1996**, *124*, 289242s.

## β-D-Galactose pentapivalate, 98%

**63,247-3** — 1g, 5g



This fully protected carbohydrate is a convenient precursor for 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine, a useful chiral auxiliary for chiral α-amino nitrile preparation via the Strecker synthesis.

Kunz, H. et al. *Tetrahedron Lett.* **1988**, *29*, 4397.

## 6-Chloropyran-2-one, 97%

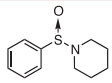
**63,299-6** — 1g, 5g

Has been used as a starting material for alkynylpyranones,[1] and for a wide spectrum of biologically active substrates including pretetramides.[2]

(1) Biagetti, M. et al. *Tetrahedron Lett.* **2003**, *44*, 607. (2) Gilbreath, G. S. et al. *J. Am. Chem. Soc.* **1988**, *110*, 6172.

## 1-Benzenesulfinylpiperidine, 97%

**63,023-3** — 1g, 5g

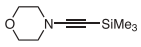


Novel reagent for the synthesis of glycosides from thioglycoside donors in high yields and excellent stereoselectivities.

Crich, D.; Li, H. *J. Org. Chem.* **2002**, *67*, 4640.

## 4-(Trimethylsilylethynyl)morpholine, 97%

**63,277-5** — 1g, 10g

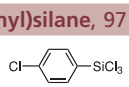


Employed in the Lewis acid mediated ring opening of terminal epoxides leading to the corresponding γ-butanolides.

Movassaghi, M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2456.

## Trichloro(4-chlorophenyl)silane, 97%

**63,045-4** — 1g, 5g



Employed as a starting material in the synthesis of tripod-shaped oligophenylenes designed for thin-film applications.

Deng, X.; Cai, C. *Tetrahedron Lett.* **2003**, *44*, 815.

*Please see pages 90–91 for additional new products.*

# Aldrichimica ACTA

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# About Our Cover

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

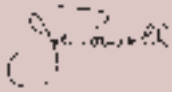
*Autumn—On the Hudson River* (oil on canvas, 151.8 x 274.9 cm) was signed and dated by the American painter Jasper Francis Cropsey in 1860. This enormous painting represents a panoramic view of the Hudson River valley about 60 miles north of New York City near West Point and Storm King Mountain.

At first glance, this landscape, painted in brilliant autumnal colors under a magnificent sunlit sky, may appear to show nature in a completely wild state. Mankind is not entirely absent, however. In the foreground and left of center, three hunters and their dogs have stopped to rest; a log cabin sits among the trees in the middle distance on the right; a town can be seen along the bank of the river; and a number of boats, including a steamer, are on the river itself. The setting is neither completely untouched by man nor overly domesticated. Man may at first seem dwarfed by nature, but is shown here to take his place harmoniously in the natural world.

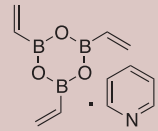
More than simply a visual record of a certain time and place, however, this painting embodies certain ideas that were current in nineteenth-century America. The natural world was thought to be the most profound manifestation of the Divine order. Moreover, the magnificence of the American landscape came to signify the expansionist ideal and the opportunities and potential greatness of this new country. The critics praised the picture extravagantly when it was exhibited in London, where it was painted from memory and from sketches brought from America during the second of two study trips the artist made to Europe. Viewers, however, questioned the brilliant colors of the foliage represented in the painting, which were more intense than anything they had ever seen. Cropsey, however, had thought to bring from America samples of brightly colored autumn leaves pasted on cardboard to demonstrate that his painting was not an exaggeration, but was quite true to nature, at least in America.

**This painting is a gift of the Avalon Foundation to the National Gallery of Art, Washington, DC.**

# "Please Bother Us."



Joe Porwoll, President



Professor Donal F. O'Shea of the Department of Chemistry at University College Dublin kindly suggested that we offer 2,4,6-trivinylcyclotriboroxane-pyridine complex. This stable vinylboronic acid equivalent undergoes facile Suzuki cross-coupling with aryl halides to provide valuable functionalized styrene derivatives.

Kerins, F.; O'Shea, D. F. *J. Org. Chem.* **2002**, *67*, 4968.

**63,799-8**
**Vinyl boronic anhydride-pyridine complex**

**56,814-7**
**Vinylboronic acid dibutyl ester, 97%**

**63,334-8**
**Vinylboronic acid pinacol ester, 95%**

Naturally, we made not only this reagent but also two other stable vinylboronic acid esters—vinylboronic acid dibutyl ester and vinylboronic acid pinacol ester—which are useful for the Suzuki coupling, Heck coupling, and Grubb's olefin cross-metathesis reactions. It was no bother at all, just a pleasure to be able to help.

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

## Table of Contents

# Lab Notes

## A Funnel Assembly for the Safe Disposal of Nitrogen Discharged from an NMR Magnet during Cryogen Refilling

In NMR laboratories, where large volumes of cryogens are routinely dispensed, a condition of displacement or deprivation of atmospheric oxygen may occur if the released gases are not efficiently removed. There is at least one reported case of displacement of oxygen by nitrogen during the installation of a magnetic resonance imaging system causing the death of a worker by asphyxiation.[1] In addition, similar incidents of asphyxiation resulting from unsafe handling of liquid nitrogen have been reported in other laboratory settings.[2,3] In setting up a Bruker 400 MHz NMR instrument in our laboratory, we were constrained to install the magnet as well as the ancillary LC-NMR components in a 6 ½ '-deep well and the computers at the main level of the room. The well and the main level of the room were equipped with ZoneGuard sensors (Biosystems Inc., Middletown, CT) for a constant monitoring of the well and room oxygen levels. The monitoring systems were set to activate an audible alarm if the oxygen level dropped to 19.5% from the normal reading of 20.9%. During refilling of the magnet with liquid nitrogen, the oxygen level in the well dropped below the danger level of 18.0% and the alarm rang continuously.[4] To minimize the risk of oxygen displacement, we explored the possibility of diverting the flow of cold nitrogen gas exiting the magnet into an area outside the NMR room. To accomplish this goal, we have fabricated a funnel assembly (**Figure 1**) for efficiently capturing and disposing of nitrogen gas and for maintaining safe oxygen levels in the room.

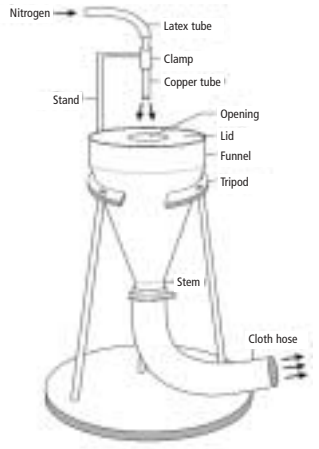



**Figure 1**. Schematic Diagram of the Funnel Assembly.

The assembly consists of a funnel mounted on a tripod, a clamp supported by the funnel, and a flexible hose attached to the stem of the funnel—as shown in the figure.[5] The mouth of the funnel is sealed with a lid that has a circular opening (3" diam) at its center, and through which the nitrogen stream enters the funnel's chamber. The internal diameter of the funnel at the lid is 9" and that of the stem 2¾" and, at 2" into its depth, the funnel's body gradually begins to narrow along the 8"-long curvature. The length of the funnel, including the two-inch-long stem, is 12" and its capacity is adequate to capture the nitrogen gas emitted from the NMR magnet during refilling. The clamp (4" long x ¼" thick) is supported by a stand (7" high x ¼" thick) welded to the rim of the funnel. A copper tube (7" long x ⅜" i.d.) is clamped in an upright position to deliver the nitrogen gas at the center of the funnel. The tip of the copper tube is positioned approximately 3" above the opening in the funnel lid, and its top end is attached to a latex tube (5' long x ⅜" i.d.) that receives nitrogen gas from the magnet. The supporting tripod consists of a partial O-ring (7" i.d.) mounted on top of 3 legs (16" high), which are fastened to a heavy circular base (14" diam). The O-ring has a 3½"-wide slit through which the funnel along with its attached stand can be readily dismounted from the tripod whenever needed. The material used for the fabrication of the funnel is nonmagnetic stainless steel, whereas that of the tripod is aluminum. The stem of the funnel is connected to a cloth hose (14' long x 3" i.d.) for carrying nitrogen gas into an exhaust line. The figure shows a segment of the latex tubing carrying nitrogen into the funnel and of the cloth hose discharging the gas.

Before liquid-nitrogen refilling, the funnel assembly is placed near the magnet and the funnel's latex tubing is connected to the left-hand-side turret. During refilling of the magnet, the funnel collects the gas discharge with no significant diffusion into the air. As it is denser than air, cold nitrogen gas settles well in the funnel and flows through the hose without applying suction. It also appears that the force of nitrogen streaming through the circular opening prevents back diffusion and exerts pressure sufficient to cause expulsion of the gas from the funnel through the hose. The gas is discharged near an exhaust line located in the well. When the magnet is full, liquid nitrogen spraying into the funnel is clearly visible from several feet away. There is practically no drop in the oxygen level in the well or in the rest of the room during the refilling procedure, suggesting efficient trapping and disposal of nitrogen by this device. Occasionally, water condenses in the first two-foot segment (from the stem of the funnel) of the exterior of the cloth hose carrying the cold gas; placing an absorbent pad underneath the hose takes care of this problem.

The funnel assembly helps in maintaining the room oxygen level during refilling of the NMR magnet with liquid nitrogen, especially if the room is not spacious or not adequately ventilated. In addition, it minimizes the chances of spillage of the cryogen and thus accidental freezing of the O-rings in the base plate and top flange of the magnet cryostat. (If freezing occurs, the sealing O-rings will be hardened leading to loss of vacuum between the casings of the magnet cryostat.) Certain modifications of the funnel assembly may be needed depending on the room's configuration or on whether added efficiency in the removal of nitrogen gas is warranted. For instance, if an exhaust line is not accessible, the delivery end of the hose may be placed outside the room for safe disposal of the gas. If improved gas flow is needed, a suction fan may be attached at the delivery end of the hose.

**References and Notes:** (1) Gill, J.R.; Ely, S.F.; Hua, Z. Environmental gas displacement: three accidental deaths in the workplace. *Am. J. Forensic Med. Pathol*. **2002**, *23*, 26; abstract available at the National Library of Medicine website at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi (accessed March 2003). (2) Kernbach-Wighton, G.; Kijewski, H.; Schwanke, P.; Saur, P.; Sprung, R. Clinical and morphological aspects of death due to liquid nitrogen. *Int. J. Legal Med.* **1998**, *111*, 191. (3) Tabata, N.; Funayama, M.; Ikeda, T.; Azumi, J.-i.; Morita, M. On an accident by liquid nitrogen—histological changes of skin in cold. *Forensic Sci. Int.* **1995**, *76*, 61. (4) Aside from recommending the installation of oxygen sensors, the manufacturer does not provide any device or recommend any procedure for handling the nitrogen discharged from the magnet during cryogen refilling. (5) The funnel, stand, and clamp were fabricated by Atlantic Sheet Metal Manufacturing (Essex, MD). The tripod was fabricated at the Division of Engineering Services, National Institutes of Health (Bethesda, MD). The entire assembly can be readily fabricated in any workshop using nonmagnetic metal sheets and rods (e.g., aluminum, copper, or nonmagnetic stainless steel) and cloth hose.

**H. Umesha Shetty** (Ph.D.),* **Jinsoo Hong**, and **Victor W. Pike**
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***Editor's Note:*** *Caution*. The potential user of this note should carefully evaluate its suitability for a particular application, as well as familiarize himself/herself with any potential hazards associated with the construction and use of this assembly. The procedure described in this note has not been tested by Sigma-Aldrich scientists. Its publication in this magazine should not be construed as being endorsed or recommended by Sigma-Aldrich.

# Organosilicon Reagents: Synthesis and Application to Palladium-Catalyzed Cross-Coupling Reactions

*Scott E. Denmark* and Michael H. Ober*
*Roger Adams Laboratory*
*Department of Chemistry*
*University of Illinois*
*Urbana, IL 61801, USA*
*Email: denmark@scs.uiuc.edu*

## Outline



Professor Scott E. Denmark (left) receiving the *2003 ACS Award for Creative Work in Synthetic Organic Chemistry* from Dr. Chris D. Hewitt, Aldrich Vice President of Marketing and R&D. Photo © James Tkatch.

Michael H. Ober

## 1. Introduction

Transition-metal-catalyzed cross-coupling of organometallic reagents with organic halides has become a powerful method for carbon–carbon-bond formation. Organotin,[1] organoboron,[2] and organozinc[3] reagents are well established as competent precursors for palladium-catalyzed cross-coupling reactions, and have found wide application in synthetic organic chemistry. But, due to a number of drawbacks inherent to these substrates, organosilicon reagents have emerged as competitive alternatives. The lack of toxicity, high chemical stability, and low molecular weight of organosilanes make them ideal for use as nucleophilic partners in cross-coupling with organic halides and pseudohalides. Silicon-based reagents were originally considered to be insufficiently active toward palladium-catalyzed cross-coupling, but early work by Hiyama et al. showed that organosilanes could be activated by a nucleophilic promoter.[4] Following this discovery, a multitude of organosilanes bearing a wide variety of substituents about the silicon center as well as an assortment of transferable groups have been identified.[5] This review will concentrate on recent advances in the use of organosilanes in palladium-catalyzed cross-coupling reactions, with an emphasis on the preparative

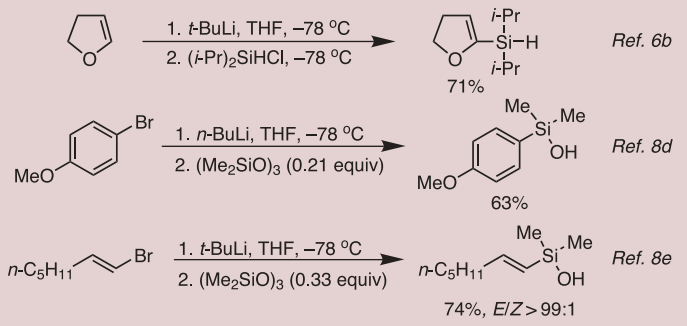



**Figure 1**. Preparation of Organosilanes by Reaction of Organometallic Reagents with Halosilanes or Cyclosiloxanes.

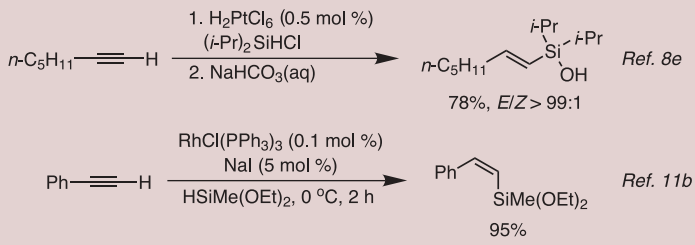



**Figure 2**. Preparation of Organosilanes by Hydrosilylation of Alkynes.

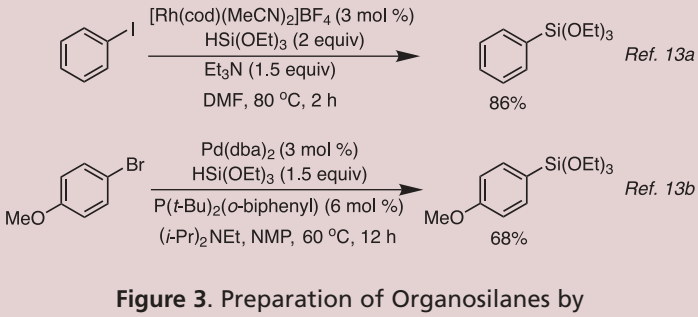



**Figure 3**. Preparation of Organosilanes by Transition-Metal-Catalyzed Coupling of Aryl Halides with Silyl Hydrides.

aspects of this chemistry and on the synthesis and applications of these substrates.

## 2. Synthesis of Organosilicon Reagents

In response to the growing interest in the palladium-catalyzed cross-coupling of organosilicon compounds, a number of methods to prepare a wide range of coupling precursors are now available. The preparations of these compounds are diverse, and are based on the type of organic moiety being employed as well as the substituents about the silicon atom. Of the methods described, most can be preformed on a large scale to provide useful quantities of material thanks, in large measure, to the relatively low cost and availability of the silicon-containing starting materials. Once synthesized, organosilanes are stable compounds that can be purified by chromatography or distillation and can be easily handled in most cases.

### 2.1. Reaction of Organometallic Reagents with Halosilanes or Cyclosiloxanes

The use of organolithium and organomagnesium reagents for the nucleophilic displacement of a leaving group at the silicon center is one of the simplest methods to introduce silicon into an organic molecule (**Figure 1**). The reaction of phenyllithium or vinylmagnesium bromide with a dialkylchlorosilane[6] readily provides the corresponding aryl- or vinylsilyl hydride. The newly formed silyl hydride can then be subjected to further manipulations to gain access to silyl ethers, silyl halides, and silanols.[6,7] Direct formation of organosilanols can be similarly accomplished by addition of the organometallic reagent to a number of readily available and inexpensive *cyclo*-siloxanes.[8] Aqueous hydrolysis of the substituted polysiloxane formed in situ provides the organosilanol, which can then be easily purified by column chromatography or distillation. Although this method of synthesis is both straightforward and efficient, it is limited by substrate compatibility with the organometallic agent employed. This problem can be avoided by protection of the sensitive functional group or, better still, by use of one of the alternative methods described below.

### 2.2. Hydrosilylation of Alkynes and Alkenes

The metal-catalyzed hydrosilylation of alkynes and alkenes to provide substituted alkenylsilanes and alkylsilanes avoids the use of highly reactive organometallic reagents and the limitations associated with them.[9] The insertion of a platinum,[8e,10] rhodium,[11] or ruthenium[12] catalyst into an Si–H bond, provides an active metal hydride that undergoes addition across an unsaturated organic precursor generating an organosilyl halide or organosilyl ether (**Figure 2**). As with the previous method, the organosilicon compounds thus generated can be further manipulated to obtain organosilanols or other silicon species. The stereo- and regioselectivity of the hydrosilylation are dependent on the catalyst employed and the silicon precursor involved in the reaction, but a judicious choice of the two agents can lead to high levels of control in most cases.[9] Obviously, this method is well suited for the preparation of alkenylsilanes and alkylsilanes. Other methods are needed to install the silicon functionality into aryl or heteroaryl subunits.

### 2.3. Transition-Metal-Catalyzed Coupling of Aryl Halides with Silyl Hydrides

Recently, investigations into the transition-metal-catalyzed coupling of organic halides with silyl hydrides have provided a powerful method for the synthesis of organosilanes. Base-activated insertion of a transition-metal complex into an Si–H bond

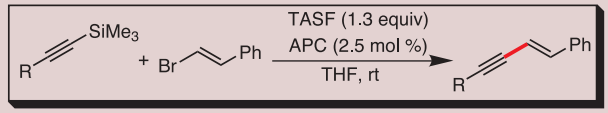
followed by transfer of the silyl group to an aryl or vinyl halide successfully provide the desired organosilane (**Figure 3**).[13] This reaction is limited to the coupling of alkoxysilanes, alkylsilanes, and halosilanes with electron-rich aryl iodides and bromides. The process is catalyzed by $Pd(dba)_2$[13b,c] or $[Rh(cod)(MeCN)_2]BF_4$[13a] in the presence of a stoichiometric amount of base, and is thought to proceed through Si–H/C–I bond exchange by oxidative addition of the hydrosilane followed by σ-bond metathesis of the Si–Pd/C–I bonds.[13c]

## 3. Palladium-Catalyzed Cross-Coupling

The coupling of organosilicon reagents with organic halides and pseudohalides has evolved to be comparable in scope to other palladium-catalyzed coupling methods.[4,5] Generally, the conditions for the palladium-catalyzed cross-coupling are mild, but do require a promoter [tetrabutylammonium fluoride (TBAF), tetramethylammonium fluoride (TMAF), tris(diethylamino)sulfonium trimethyldifluorosilicate (TASF), potassium trimethylsilanolate (TMSOK), $Ag_2O$, $Cs_2CO_3$, etc.] to provide high yields of the desired cross-coupling products. The byproducts of the cross-coupling reaction are polysiloxanes, which can be removed by conventional methods such as chromatography (silica gel or reverse-phase) or distillation. Many types of organosilanes are competent coupling partners for the palladium-catalyzed reaction. The following survey of silicon-containing cross-coupling components is organized around three principal rubrics: (1) the type of transferable group on the organosilane, (2) the method of organosilane activation, and (3) the nontransferable substituents about the silicon center.

### 3.1. Alkynylsilanes

The palladium-catalyzed coupling reaction of terminal alkynes developed by Sonogashira and co-workers has been widely applied in many synthetic endeavors.[14] Nevertheless, new general methods that employ mild conditions are still of great interest for the synthesis of substituted alkynes. Alkynyl(trialkyl)silanes and alkynylsilanols, which are easily synthesized by addition of alkynyllithium reagents to chlorosilanes, are competent reagents for the palladium-catalyzed cross-coupling reaction.[15] The successful coupling of substituted trimethylsilylethynes with aryl or vinyl iodides or with vinyl bromides requires the use of 1.3 equiv of TASF and 2.5 mol % of




eq 1

APC = allylpalladium chloride dimer, $[\pi\text{-allylPdCl}_2]_2$
TASF = tris(diethylamino)sulfonium trimethyldifluorosilicate

*Ref. 15a*

| R | Yield |
|---|---|
| Ph | 83% |
| $n\text{-}C_5H_{11}$ | 86% |
| $CH_2OH$ | 84% |

$[\pi\text{-allylPdCl}_2]_2$ (APC) in THF at ambient temperature, to provide substituted alkynes in good yields (**eq 1**).[15a] Catalytic amounts of CuCl or CuCl–$Pd(PPh_3)_4$ can also be used at elevated temperatures in DMF to effect the coupling of alkynyl(trialkyl)silanes with aryl chlorides or triflates.[15b] Alternatively, dimethyl(phenylethynyl)silanol undergoes facile coupling with aryl iodides in THF at 60 ˚C in the presence of a stoichiometric amount of TBAF or $Ag_2O$ and 5 mol % of $Pd(PPh_3)_4$.[15c]

### 3.2. Alkenylsilanes

The palladium-catalyzed cross-coupling of alkenylsilanes with organic halides and pseudohalides has gained much attention because of the mild reaction conditions required and broad scope of olefinic products that can be obtained.[4,5] In general, the cross-coupling reactions of alkenylsilanes are highly efficient, but several side processes can intervene under the reaction conditions. Of these undesirable processes, the most notable are the unproductive removal of the silicon moiety (protodesilylation) and the formation of undesired regioisomers. In most cases, manipulation of the reaction conditions (choice of promoter, palladium catalyst, and ligands) can avoid many of these pitfalls to provide high-yielding and selective reactions.

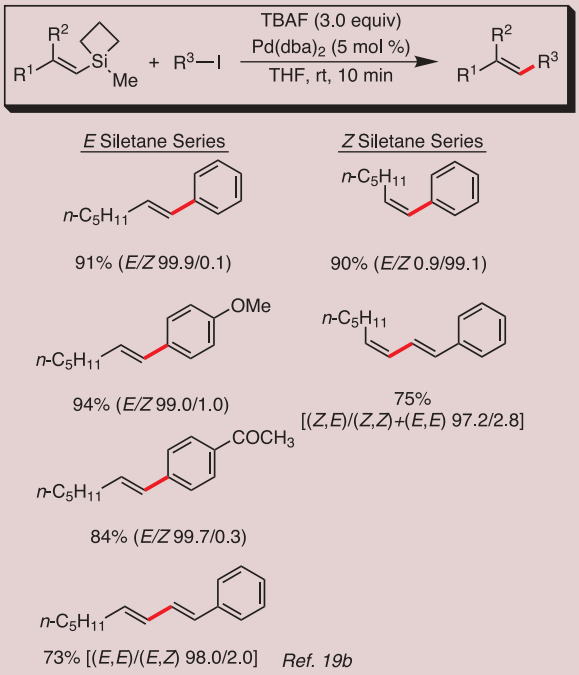
#### 3.2.1. Fluoride Activation

Because of the high affinity of fluoride for silicon (BDE Si–F = 135 kcal/mol),[16] the use of a fluoride ion source (in the form of TBAF, TMAF, TASF, KF, or CsF) together with tetracoordinate silanes is believed to provide pentacoordinate fluorosiliconate intermediates, which are considered to be the "active" species in the palladium-catalyzed cross-coupling reactions.[4] Silicon-29 NMR spectroscopic studies on the use of TBAF as a promoter for the palladium-catalyzed cross-coupling of several types of alkenylsilanes (alkenylsiletanes, alkenylsilyl halides, alkenylalkoxysilanes, alkenyldisiloxanes, and alkenylsilanols) provide that all of these precursors react via a common intermediate, hypothesized to be a hydrogen-bonded silanol–fluoride adduct.[17] Because of this mechanistic commonality, a wide range of organosilanes, that display a similar reactivity yet provide a variety of precursor options, are competent reagents for the fluoride-activated cross-coupling reaction.

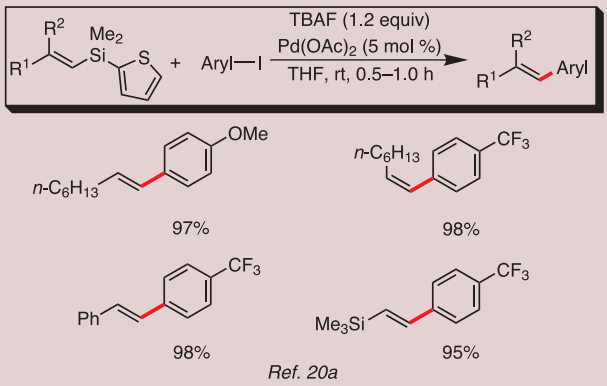
Three classes of alkenylsilanes undergo facile fluoride-promoted cross-coupling: (1) alkenylsilanes bearing alkyl groups on the silicon, (2) alkenylsilanes bearing fluoride-cleavable organic groups (alkenylsilanol surrogates), and (3) heteroatom-substituted alkenylsilanes. In general, alkyl-substituted alkenylsilanes are extremely stable to chemical manipulations prior to fluoride activation, but do not readily undergo productive cross-coupling. Alkenylsilanol surrogates are also stable under conditions for many reactions. However, these silanes contain a cleavable group that, in the presence of a fluoride activator, produces a heteroatom-substituted alkenylsilane in situ, which provides a compromise of stability and reactivity. Heteroatom-substituted alkenylsilanes are, of all the types identified here, the most reactive toward palladium-catalyzed cross-coupling due to the ease with which they can access an "active" species under fluoride promotion. Unfortunately, these silanes are also the most labile toward unproductive reactions including hydrolysis, protodesilylation, and dimerization and, therefore, must be promptly subjected to palladium-catalyzed cross-coupling without prior chemical manipulations. Thoughtful selection of the alkenylsilanes and the reactions in which they can be employed leads to a balanced combination of precursor and conditions, allowing for a wide range of olefinic cross-coupling products.

##### 3.2.1.1. Alkenyl(trialkyl)silanes

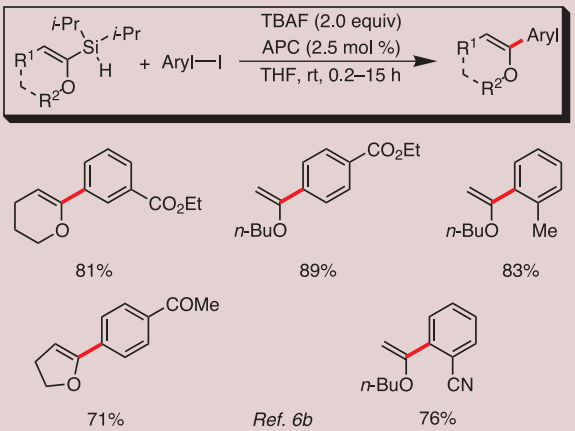
The combination of readily available trimethyl(vinyl)silane and an aryl iodide, under somewhat modified conditions to those developed for alkynyl(trialkyl)silanes mentioned previously (2.4 equiv of TASF and 5 mol % of $Pd(PPh_3)_4$ in THF at 50 ˚C),




**eq 2**




**eq 3**




**eq 4**

is effective for the production of vinylated products. The reaction is tolerant of diverse functionality on the aryl iodide, but substitution on the trimethyl(vinyl)silane inhibits productive cross-coupling. The failure to engage substituted alkenyl(trialkyl)silanes in this process is believed to arise from their inability to form the required pentacoordinate fluorosiliconate species.[18]

### *3.2.1.2. Alkenylsilanol Surrogates*

#### 3.2.1.2.1. Alkenylsiletanes

Alkenylsilacyclobutanes represent a special class of alkenyl(trialkyl)silanes that can undergo facile palladium-catalyzed cross-coupling with aryl and vinyl iodides. These reactions proceed rapidly in the presence of 3 equiv of TBAF and 5 mol % of $Pd(dba)_2$ in THF at ambient temperature (**eq 2**).[19] Alkenylsiletanes, which can be readily prepared from organometallic addition to 1-chloro-1-methylsilacylobutane,[19b] originally were thought to undergo cross-coupling this rapidly due to the enhanced Lewis acidity of the silicon center from strain release during the formation of the pentacoordinate fluorosiliconate.[19c] However, under the reaction conditions, the siletanes are observed to undergo a fast initial ring opening to form alkenyl(propyl)(methyl)silanols, which are most likely the active species for the cross-coupling reaction.[17] Direct comparisons to alkenylsilanols, alkenylsilyl halides, and alkenylsilyl ethers reveal a similar reactivity, and corroborate the observation that these alkenylsilanes react via the same intermediate.[17]

#### 3.2.1.2.2. Alkenyl(thienyl)- and Alkenyl(pyridyl)silanes

The observation that 2-thienyl and 2-pyridyl groups on silicon are not transferred to organic halides under standard palladium-catalyzed cross-coupling conditions, combined with the fact that at least one activating group or heteroatom is required on the silicon center to provide the coupling product, prompted the investigation of alkenyldimethyl(2-thienyl)silanes and alkenyldimethyl(2-pyridyl)silanes. These compounds are considered excellent cross-coupling substrates due to the enhanced stability provided by the heterocyclic groups toward moisture, acid, and base as compared to the corresponding halosilanes or other heteroatom-substituted silanes.[20a] This allows for the alkenylsilane coupling precursors to resist some chemical manipulations prior to palladium-catalyzed cross-coupling. Alkenyldimethyl(2-thienyl)silanes undergo cross-

coupling with a number of aryl iodides and bromides in the presence of 1.2 equiv of TBAF and 5 mol % of $Pd(OAc)_2$ in THF at ambient temperature (**eq 3**).[20a] Similarly, alkenyldimethyl(2-pyridyl)silanes afford cross-coupling products from aryl and vinyl iodides at slightly elevated temperatures.[20b,c]

#### 3.2.1.2.3. Alkenyl(benzyl)silanes

Benzyldimethylsilyl-substituted alkenes are similar to the aforementioned 2-thienyl- and 2-pyridylsilanes in that the benzyl group is also considered non-transferable. In addition, it is stable to acid, buffered fluoride medium, and strong base. However, the benzyl substituent does suffer rapid cleavage with 2.2 equiv of TBAF in THF at 0 °C to provide the corresponding silanol. Accordingly, benzyldimethylsilanes are expected to possess enhanced chemical stability compared to heteroaryl-containing silanes and yet still be activated with TBAF for cross-coupling.[21]

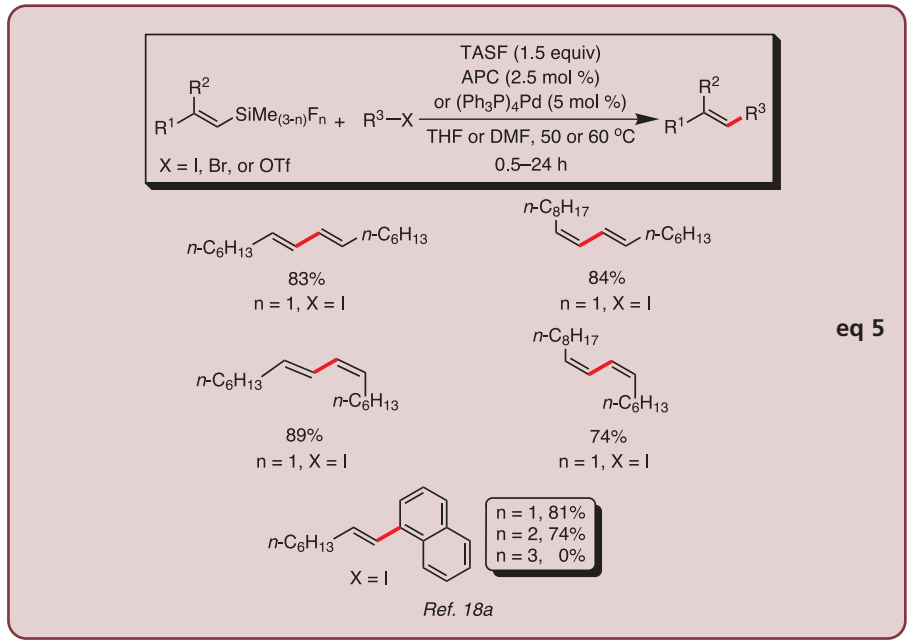
#### 3.2.1.2.4. Alkenylsilyl Hydrides

Silyl hydrides, which are easily synthesized through organometallic addition to dialkylchlorosilanes, are more stable to hydrolysis than are the heteroaryl-substituted organosilanes. In addition, they have lower molecular weights compared to other non-heteroaryl-substituted organosilanes and are thus ideal for use with sensitive or precious substrates. These characteristics are illustrated in the palladium-catalyzed cross-coupling of 2-(4,5-dihydrofuranyl)-diisopropylsilane and 2-(5,6-dihydro-4*H*-pyranyl)diisopropylsilane These alkenylsilyl hydrides undergo oxidative hydrolysis when combined with TBAF•$3H_2O$, producing the alkenylsilanols in situ.[22] Indeed, the corresponding silanols give similar results under identical conditions. A number of (α-alkoxyvinyl)silyl hydrides are effective cross-coupling agents when combined with aryl iodides in the presence of 2 equiv of TBAF and 2.5 mol % of APC in THF at room temperature (**eq 4**).[6b] The reaction is compatible with a broad range of functional groups, and manipulation of the intermediate alkoxy vinyl ethers with 1 N HCl provides the corresponding ketones directly.[6b]

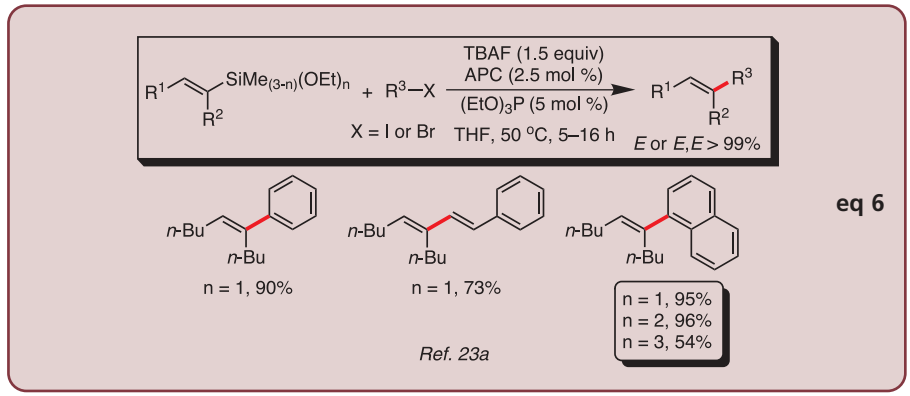
### *3.2.1.3. Heteroatom-Substituted Alkenylsilanes*

#### 3.2.1.3.1. Alkenylsilyl Halides

Alkenylsilyl chlorides and fluorides were among the first alkenylsilanes to act as effective and general substrates in the palladium-catalyzed cross-coupling reaction.[4] The combination of halo(alkyl)silanes or dihalo(alkyl)silanes with organic halides in the presence of 1.5 equiv of TASF and 2.5 mol % of APC in THF at 50 °C or, alternatively, with 5 mol % of $(Ph_3P)_4Pd$ in DMF at 60 °C provides the desired cross-coupling products in good yields (**eq 5**).[18a] Many organic halides and pseudohalides are suitable as coupling partners, and the reaction is highly stereo- and regioselective in the case of (*E*)- and (*Z*)-fluoro(dimethyl)silyl-1-alkenes. Interestingly, trihalosilanes are ineffective in the cross-coupling reaction of 1-iodonaphthalene, but do function in the coupling with an alkenyl triflate.[18b]




**eq 5**



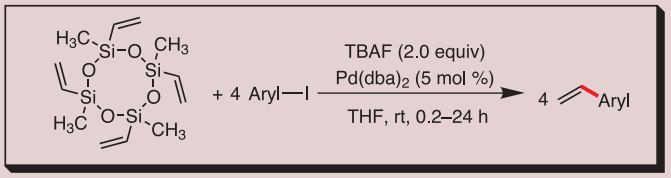

**eq 6**

#### 3.2.1.3.2. Alkenyl(alkoxy)silanes

Alkenyl(alkoxy)silanes (silyl ethers) react at rates comparable to those of alkenylsilanols and alkenylsilyl halides with similar numbers of heteroatoms about the silicon center, but are less prone to hydrolysis or oligomerization. Alkenylmono-, di-, and trialkoxysilanes—in the presence of 1.5 equiv of TBAF, 2.5 mol % of APC, and 5 mol % of $(EtO)_3P$ in THF at 50 °C—undergo cross-coupling with a number of organic halides (**eq 6**).[23a] Vinyltrimethylsiloxane has also proved useful as a vinyl transfer agent for aryl iodides.[23b]

#### 3.2.1.3.3. Alkenyldisiloxanes and Poly(alkenylsiloxanes)

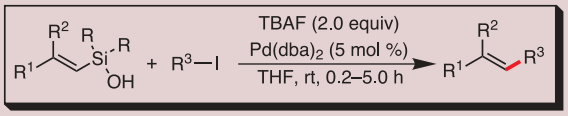
Alkenyldisiloxanes are readily formed by dehydrative dimerization of their parent alkenylsilanols with a catalytic amount of base.[17] The disiloxane moiety is thermodynamically stable, making alkenyldisiloxanes one of the more easily handled types of organosilicon compound. Because they converge to the same intermediate in the presence of TBAF as the corresponding alkenylsilanols, alkenyldisiloxanes undergo cross-coupling with the same outcome.[17] Similarly, the readily available siloxane oligomers also provide productive cross-coupling with

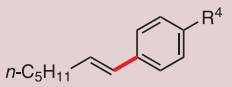



| Aryl: | 2-MeOC$_6$H$_4$ | 4-MeOC$_6$H$_4$ | 3-NO$_2$C$_6$H$_4$ | 4-CH$_3$COC$_6$H$_4$ | 4-EtO$_2$CC$_6$H$_4$ |
|---|---|---|---|---|---|
| Yield: | 72% | 63% | 87% | 88% | 85% |

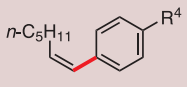
*Ref. 24b*

**eq 7**

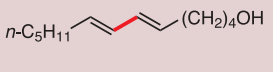


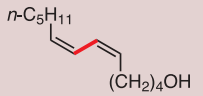
R = Me, R$^4$ = MeO: 95% (*E*/*Z* 97.2/2.8)
R = *i*-Pr, R$^4$ = Ac: 80% (*E*/*Z* 99.5/0.5)



R = Me, R$^4$ = MeO: 94% (*E*/*Z* 2.6/97.4)
R = *i*-Pr, R$^4$ = Ac: 86% (*E*/*Z* 1.0/99.0)



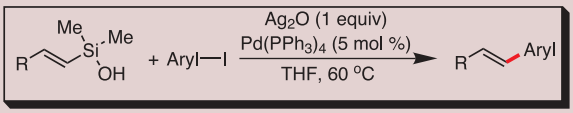
R = Me: 91% [(*E*,*E*)/(*E*,*Z*) 95.8/4.2]
R = *i*-Pr: 87% [(*E*,*E*)/α-isomer 97.8/2.2]
α-isomer = cine-rearranged product

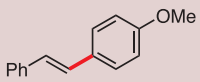


R = Me: 64% [(*Z*,*Z*)/AOI 87.8/12.2]
R = *i*-Pr: 68% [(*Z*,*Z*)/AOI 92.4/7.6]
AOI = all other isomers

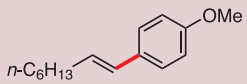
*Ref. 8e*

**eq 8**



67%, 3 h



95%, 4 h

*Ref. 26a*

**eq 9**

TBAF activation. Poly(alkenylsiloxanes) are easily synthesized by hydrosilylation of terminal alkynes with poly(methylhydrosiloxane) (PMHS) and a catalytic amount of $(Bu_4N)_2PtCl_6$. Cross-coupling of poly(alkenylsiloxanes) with a number of aryl iodides proceeds smoothly with 5 equiv of the polysiloxane, 1.2 equiv of TBAF, and 2.5 mol % of $Pd_2(dba)_3$•$CHCl_3$ in THF at 60 °C.[24a] Several commercially available cyclooligodisiloxanes, orthosiliconates, and disiloxanes are extremely efficient vinyl transfer agents for a broad range of aryl iodides with 2–3 equiv of TBAF and 1–5 mol % of $Pd(dba)_2$ in THF at ambient temperature.[24b] 1,3,5,7-Tetravinyl-1,3,5,7-tetramethylcyclotetrasiloxane is the most competent of the vinyl transfer agents under these conditions, allowing all of the possible vinyl groups to transfer during the cross-coupling reaction (**eq 7**). This reaction is general and, due to the inexpensive and nontoxic nature of the starting materials, amenable to large-scale preparations.[24b]

#### 3.2.1.3.4. Alkenylsilanols

Alkenylsilanols are excellent substrates for the palladium-catalyzed cross-coupling reaction when activated by TBAF. Alkenyl(dimethyl)silanols and alkenyl(diisopropyl)silanols couple rapidly with a large number of aryl and vinyl iodides in the presence of 2 equiv of TBAF and 5 mol % of $Pd(dba)_2$ in THF at ambient temperature (**eq 8**).[8e] Highly substituted and functionalized (*E*)- and (*Z*)-alkenyl(dialkyl)silanols also undergo facile coupling, with good efficiency and high stereospecificity.[25a] The palladium-catalyzed cross-coupling of alkenyl(dimethyl)silanols with aryl and vinyl triflates and nonaflates can also be accomplished at ambient temperature by the use of a hydrated TBAF (TBAF•3–10$H_2O$) in 1,4-dioxane solution in the presence of 5 mol % of $PdBr_2$ and 10 mol % of 2-[di(*tert*-butyl)phosphino]-1,1'-biphenyl. Under these conditions, the undesired cleavage of the pseudohalide to the corresponding phenol or ketone is minimized by the increased hydration level of the TBAF solution.[25b]

### 3.2.2. Fluoride-Free Activation of Alkenylsilanols, Diols, and Triols

Tetrabutylammonium fluoride (TBAF) and other fluoride-containing reagents are highly effective for promoting the palladium-catalyzed cross-coupling of a range of organosilanes. However, the widespread use of silicon protecting groups in complex-molecule synthesis precludes the application of a fluoride-activated coupling that may jeopardize the integrity of the silicon protecting groups. Thus, a non-fluoride promoter that would facilitate the silicon-based couplings with equal efficiency and selectivity is highly desirable. The first such promoter that has been identified is silver oxide ($Ag_2O$), which can activate alkenylsilanols, diols, and triols in the presence of a palladium catalyst in THF at 60 °C (**eq 9**).[26a,b] Silver oxide is thought to act as a nucleophilic activator for the silanol to form a pentacoordinate silicate species, and to assist in halide abstraction from the palladium center thus facilitating transmetalation.[26a]

Alternatively, the inexpensive salt, potassium trimethylsilanolate (TMSOK), can also be employed for the activation of alkenyl(dimethyl)silanols.[26c,d] For example, the cross-coupling of (*E*)- and (*Z*)-1-heptenyl(dimethyl)silanols with a variety of aryl and vinyl iodides is efficiently promoted by 2 equiv of TMSOK and 5 mol % $Pd(dba)_2$ in DME at ambient temperature (**eq 10**).[26c] When activated by TMSOK, silanols are as reactive as when activated by TBAF and give rise to cross-coupling products in high yields and with excellent regio- and stereoselectivities. Direct comparison of the palladium-catalyzed cross-coupling of alkenyl(dialkyl)silanols under activation by TBAF or TMSOK reveals a striking difference in the sensitivity of the coupling rate to steric effects at the silicon center.[26d] For example, whereas under TBAF activation both alkenyldimethyl- and alkenyldiisopropylsilanols couple at the same rate, under TMSOK activation the

dimethylsilanols react nearly 20 times faster! This and other observations suggest that a different mechanism may be operating under the fluoride-free conditions. It is possible to employ other bases (e.g., KH, NaH, KO*t*-Bu, NaO*t*-Bu, or NaOH) for the palladium-catalyzed cross-coupling of alkenyl(dialkyl)-silanols, but they are not as effective nor as well studied as those already mentioned.[26b-d]

### 3.3. Arylsilanes

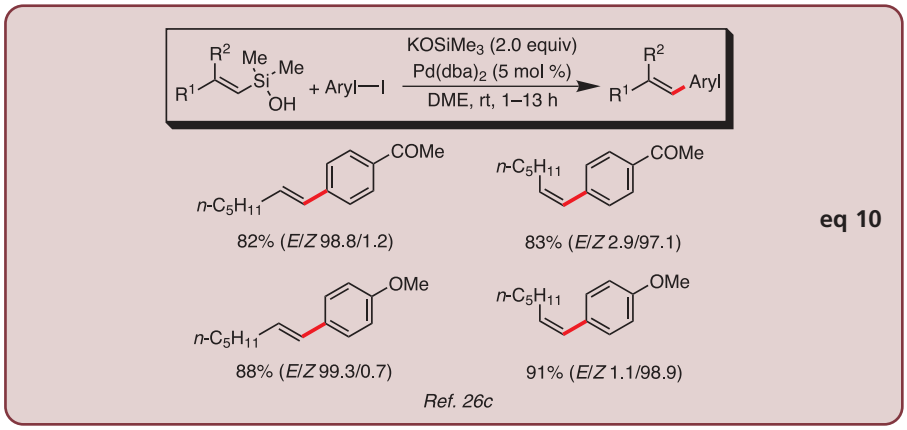
Compared to alkenylsilanes, arylsilanes have similar physical and chemical properties and may be prepared through similar synthetic routes. Unlike their alkenyl counterparts, however, arylsilanes require more forcing conditions to undergo palladium-catalyzed cross-coupling with aryl and vinyl halides. These harsher conditions often lead to undesirable side reactions such as protodesilylation and homocoupling of the organic halide.[4,5] A number of protocols have been developed to suppress or minimize the unproductive pathways and maximize the formation of the desired cross-coupling products.

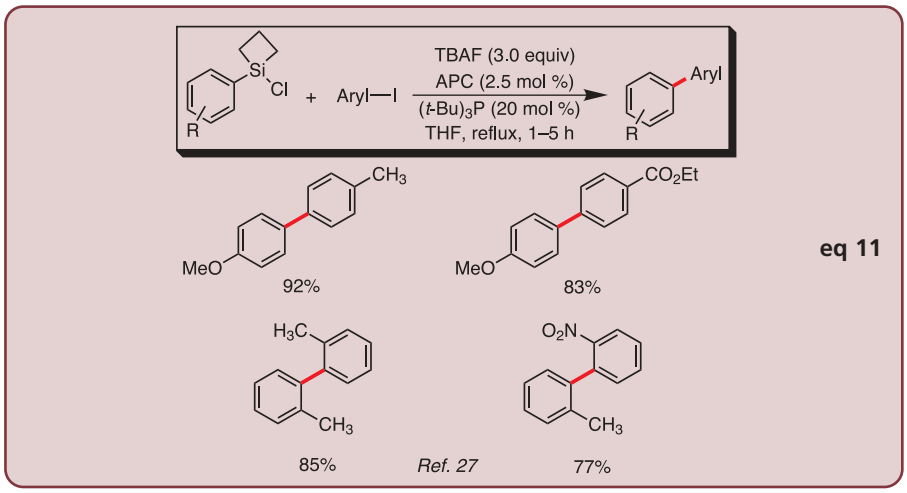
#### 3.3.1. Arylsiletanes

Unlike alkenylsilacyclobutanes, the palladium-catalyzed cross-coupling of methyl(phenyl)silacyclobutane with aryl iodides in the presence of 3 equiv of TBAF and 5 mol % of APC in refluxing THF provides no desired cross-coupling products. However, activation of the siletane by substituting a chloride or fluoride for the methyl group on the silicon allows these halo(aryl)silacyclobutanes to couple readily with aryl iodides under somewhat modified conditions (**eq 11**).[27] These conditions also provide a moderate amount of undesired homocoupling product, which can be minimized by the addition of 20 mol % of (*t*-Bu)$_3$P to the reaction mixture. The addition of the phosphine ligand to the reaction retards both the homocoupling and cross-coupling pathways, but overall provides a more favorable ratio of the two observed products. Under these conditions, both aryl(chloro)silacyclobutanes and aryl(fluoro)silacyclobutanes are competent coupling precursors, with aryl(chloro)-silacyclobutanes providing biaryl cross-coupling products with slightly extended reaction times.[27]

#### 3.3.2. Arylsilyl Halides

Palladium-catalyzed phenyl transfer to aryl iodides, bromides, and triflates can be performed with tetrabutylammonium triphenyldifluorosilicate (TBAT), an active difluorosiliconate, in the presence of 10 mol % of Pd(dba)$_2$ in DMF at 95 °C to afford unsymmetrical biaryls in good yields.[28a] The cross-coupling of substituted aryl(alkyl)-difluorosilanes with aryl iodides, bromides, and triflates takes place smoothly to provide a number of biaryls in high yields.[18b,28b,c] Aryl(alkyl)dichlorosilanes can also be employed as cross-coupling partners with aryl halides under activation with fluoride [KF, APC (5 mol %), DMF, 120 °C],[28c] or with sodium hydroxide [Pd(OAc)$_2$, Ph$_3$P, THF, 60 °C].[28d] Application to solid-phase synthesis can also be accomplished using iodobenzoic acid tethered to Wang resin.[28e]



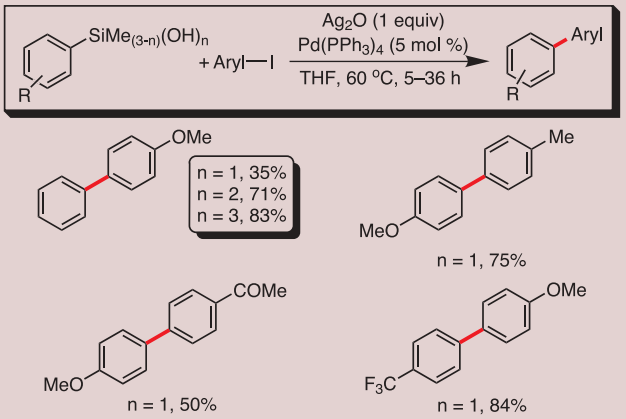




#### 3.3.3. Aryl(alkoxy)silanes

Compared to the corresponding halides, aryl(alkoxy)silanes are more stable and, in some cases, readily available. Phenyltrimethoxysilane undergoes facile palladium-catalyzed cross-coupling with aryl iodides and bromides. In the presence of 2 equiv of TBAF and 10 mol % of Pd(dba)$_2$ in DMF at 95 °C, the desired substituted benzene products are formed with little or no homocoupling byproduct observed.[23b] The cross-coupling of phenyltrimethoxysilane with aryl chlorides can also be accomplished with the addition of phosphine[29a] or N-heterocyclic carbene[29b] ligands to the reaction mixture. *Alkyl* halides can also be subjected to the palladium-catalyzed cross-coupling with substituted aryltrimethoxysilanes in the presence of 2.4 equiv of TBAF, 4 mol % of PdBr$_2$, and 10 mol % of (*t*-Bu)$_2$MeP in THF. Both alkyl iodides and bromides are competent coupling partners, and the reaction is preformed at ambient temperature to provide alkyl-substituted arenes in good yields.[29c]

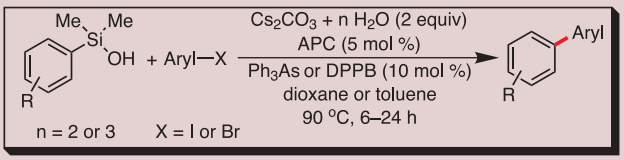
#### 3.3.4. Arylsilanols, Diols, and Triols

The preparation of arylsilanols is discussed in Section 2.1. Arylsilanediols and triols can easily be synthesized by addition of aryllithium reagents to chlorosilanes followed by careful hydrolysis of the corresponding di- and trihalosilanes. As with their alkenyl counterparts, all three types can be activated with 1 equiv of Ag$_2$O in the presence of a palladium catalyst in THF at 60 °C to give cross-coupling products with




Ref. 26a,b

**eq 12**

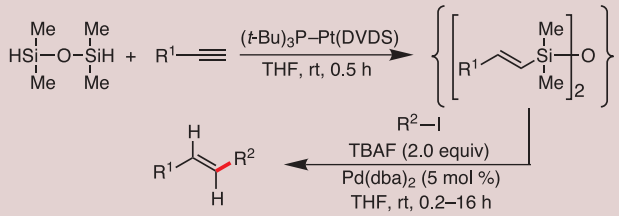



DPPB = 1,4-bis(diphenylphosphino)butane

**eq 13**

| X | R | Aryl | Yield |
|---|---|---|---|
| I | 4-MeO | 4-$MeC_6H_4$ | 90% |
| I | 4-MeO | 2-$MeC_6H_4$ | 85% |
| I | 4-MeO | 4-$EtO_2CC_6H_4$ | 87% |

Ref. 30




| $R^1$ | $R^2$ | Yield |
|---|---|---|
| *n*-$C_5H_{11}$ | 4-$MeOC_6H_4$ | 84% |
| *n*-$C_5H_{11}$ | 4-$AcC_6H_4$ | 94% |
| *n*-$C_5H_{11}$ | *n*-$C_5H_{11}CH{=}CH$ | 67% |
| Ph | 4-$MeOC_6H_4$ | 74% |
| $HO(CH_2)_3$ | 4-$MeOC_6H_4$ | 89% |

DVDS = 1,3-divinyl-1,1,3,3-tetramethyldisiloxane

Ref. 32

**Scheme 1**. One-Pot, *Inter*molecular Tandem Hydrosilylation/Cross-Coupling Reaction.

aryl iodides (**eq 12**).[26a,b] The coupling of arylsilanols with aryl iodides can also be achieved at 90 °C in dioxane by the action of 2 equiv of $Cs_2CO_3$•$2H_2O$ in the presence of 5 mol % of APC and 10 mol % of $Ph_3As$. The corresponding reaction of aryl bromides requires the use of 10 mol % of 1,4-bis(diphenylphosphino)butane (DPPB) instead of $Ph_3As$ and is carried out at 90 °C in toluene (**eq 13**).[30] Both methods provide high yields of biaryls and little or no homocoupling byproduct.

### 3.4. Alkylsilanes

Protocols for the palladium-catalyzed cross-coupling of alkylsilanes with organic halides include highly activated organosilicon reagents which allow for methyl, allyl, or alkyl cross-coupling. Methyl transfer to aryl iodides is accomplished with 2 equiv of TASF and 1.3 mol % of APC in THF at 50 °C to provide methylated cross-coupling products in good yields.[31a] More interestingly, alkyltrifluorosilanes yield cross-coupling products with aryl iodides and bromides when activated with 4 equiv of TBAF and 5 mol % of $(PPh_3)_4Pd$ in refluxing THF.[31b] Allyltrifluorosilanes couple with aryl iodides and triflates under the action of TBAF or TASF and 5 mol % of a palladium catalyst.[31c] Overall, the cross-coupling of alkylsilanes is not as well established as those of alkynyl-, alkenyl-, or arylsilanes, and few general procedures have been identified.

## 4. Tandem Reactions of Organosilicon Compounds

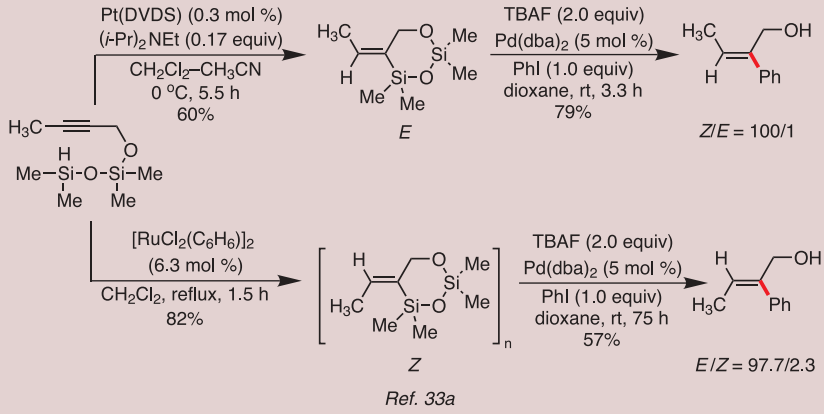
The diversity of organosilicon compounds that undergo palladium-catalyzed cross-coupling, as well as the different methods by which they can be synthesized enable a wide range of synthetic applications. Multistep or tandem reactions that harness the power of the organosilicon moiety can be effectively applied to create complex structures rapidly. These tandem reactions, terminating with palladium-catalyzed cross-coupling, highlight the advantages that silicon-based carbon–carbon-bond formation can offer to the realm of synthetic organic chemistry.

### 4.1. Intermolecular Hydrosilylation/ Cross-Coupling

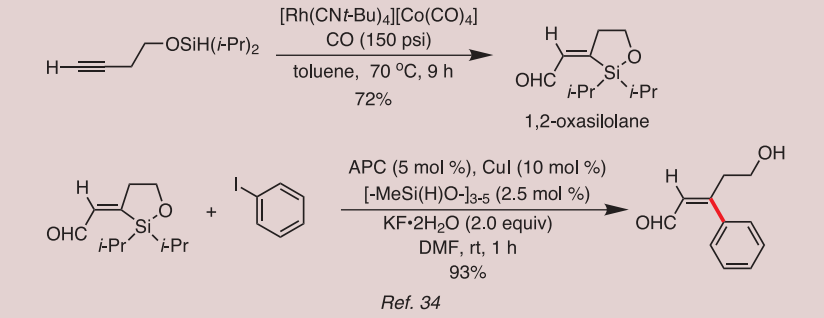
The hydrosilylation of terminal alkynes, followed by palladium-catalyzed cross-coupling of the alkenylsilane product, affords 1,2-disubstituted *E* alkenes in high yields and with high stereoselectivities. For example, a symmetrical alkenyldisiloxane can be generated by reaction of 0.5 equiv of tetramethyldisiloxane, $(t\text{-}Bu)_3P$–Pt(DVDS) with a terminal alkyne. The hydrosilylation is highly regio- and stereoselective for the production of the *E* 1-alkenyldisiloxane. The subsequent cross-coupling reaction can be performed directly on the in situ generated alkenyldisiloxane with aryl or vinyl iodide under the action of 2 equiv of TBAF and 5 mol % of $Pd(dba)_2$ to yield the desired products (**Scheme 1**).[32] This efficient Pt–Pd system effects the net hydroarylation of terminal alkynes.

### 4.2. Intramolecular Hydrosilylation/ Cross-Coupling

Starting from simple propargylic and homopropargylic alcohols, highly functionalized trisubstituted allylic and homoallylic alcohols are obtainable through an intramolecular hydrosilylation followed by a rapid palladium-catalyzed cross-coupling of the intermediate cyclosiloxanes with aryl iodides. Propargylic alcohols can easily be converted to *E* or *Z* alkenylcyclodisiloxanes under Pt(DVDS) or $[RuCl_2(C_6H_6)]_2$ catalysis, respectively, in high yields and with excellent stereo- and regioselectivities. The palladium-catalyzed cross-coupling of these cyclodisiloxanes with a number of aryl iodides (in the presence of 2 equiv of TBAF and 5 mol % of $Pd(dba)_2$ in 1,4-dioxane at ambient temperature) leads to trisubstituted *Z* or *E* allylic alcohols (**Scheme 2**).[33a] The one-pot synthesis of trisubstituted homoallylic alcohols is accomplished by treating the corresponding homopropargylic alcohol with 1 equiv of tetramethyldisilazane (TMDS), and 0.3 mol % of Pt(DVDS) in THF at ambient temperature. This provides the intermediate alkylidene-1,2-oxasilolanes, which are then treated with aryl iodides, 2.2 equiv of TBAF, and 10 mol % of $Pd(dba)_2$ to afford the trisubstituted homoallylic alcohols.[33b]




**Scheme 2**. *Intra*molecular Tandem Hydrosilylation/Cross-Coupling Reaction.




**Scheme 3**. Tandem Silylformylation/Cross-Coupling Reaction.

### 4.3. Silylformylation/ Cross-Coupling

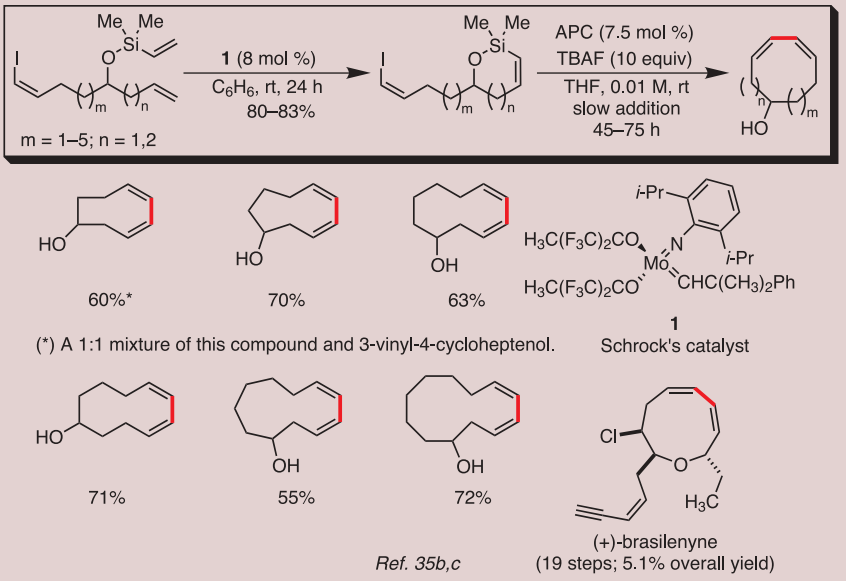
In the preceding two cases, hydrosilylation provided olefinic coupling precursors containing a newly formed carbon–silicon bond. Silylformylation, on the other hand, gives rise to new, vicinal carbon–silicon and carbon–carbon bonds to create an aldehyde-containing alkenylsilane. These compounds provide functionalized α,β-unsaturated aldehydes when subjected to the palladium-catalyzed cross-coupling. The realization of this tandem silylformylation/cross-coupling process begins with the intramolecular silylformylation of homopropargylic silyl ethers with 0.5 mol % of $[Rh(CNt\text{-}Bu)_4][Co(CO)_4]$ under 150 psi of carbon monoxide in toluene at 70 ˚C. The newly formed, aldehyde-containing, cyclic silyl ethers are competent cross-coupling partners with aryl iodides in the presence of 2 equiv of $KF•2H_2O$, 5 mol % of APC, 10 mol % of CuI, and 2.5 mol % of methylhydrocyclosiloxane in DMF at ambient temperature (**Scheme 3**). The use of both CuI and the hydrosilane are essential for the efficiency of the cross-coupling reaction and are thought to mediate the formation of the key reactive catalytic species.[34]

### 4.4. Mizoroki–Heck Reaction/Cross-Coupling

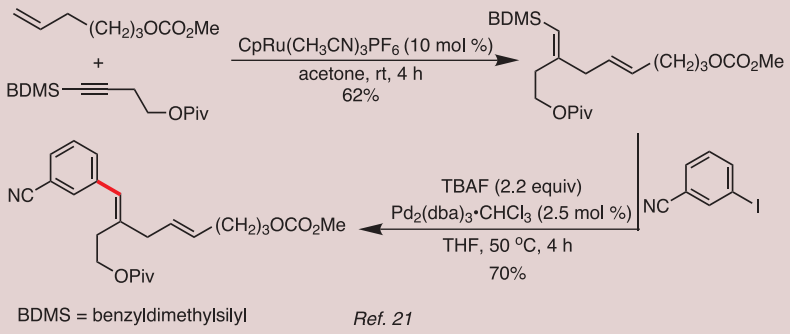
As mentioned in Section 3.2.1.2.2, the use of 2-pyridylsilanes as cross-coupling agents allows for the preservation of the silicon moiety through chemical manipulations prior to the palladium-catalyzed cross-coupling. A secondary property of the pyridyl group is that it can be employed as a directing group for the Mizoroki–Heck reaction. These two assets allow for a tandem Heck reaction/palladium-catalyzed cross-coupling reaction to afford highly substituted alkenes efficiently and in good yields. Exposure of dimethyl(hexenyl)-(2-pyridyl)silane to 0.5 mol % of $Pd_2(dba)_3•CHCl_3$, 2 mol % of tri(2-furyl)-phosphine (TFP), 1 equiv of $Et_3N$, and an aryl iodide in THF at 60 ˚C produces in situ the Mizoroki–Heck coupling product with retention of the 2-pyridylsilane unit. This intermediate, aryl-substituted dimethyl-(hexenyl)(2-pyridyl)silane can then undergo a subsequent cross-coupling reaction upon addition of 1 equiv of TBAF and a second aryl iodide to provide the olefinic products in good yields and excellent stereo- and regioselectivities.[20b,c] The selectivity of the Mizoroki–Heck process is proposed to be enhanced by the 2-pyridylsilane functionality, which directs the carbopalladation across the double bond of the alkenyldimethyl(2-pyridyl)silane.[20b]

### 4.5. Ring-Closing Metathesis/Cross-Coupling

The combination of ring-closing metathesis (RCM) and palladium-catalyzed cross-coupling constitutes a powerful sequence for the synthesis of substituted, unsaturated alcohols and medium-size rings with *cis*,*cis*-1,3-diene units. Alkenyl-(dimethyl)silyl ethers containing terminal alkenes undergo efficient ring closure in the presence of Schrock's catalyst to afford cycloalkenylsiloxanes of varying sizes. These siloxanes couple with aryl iodides in the presence of 2 equiv of TBAF and 5 mol % of $Pd(dba)_2$ in THF at room temperature to provide highly substituted styrenes in high yields.[35a] The intramolecular




**Scheme 4**. Tandem Ring-Closing Metathesis/Cross-Coupling Reaction (Yields Shown Are for the Cross-Coupling Step).




**Scheme 5**. Tandem Alder-Ene/Cross-Coupling Reaction.

variant of this reaction provides access to a number of medium-size rings,[35b] and has been exemplified in the synthesis of (+)-brasilenyne, an antifeedant isolated from *Aplysia brasiliana* (**Scheme 4**).[35c]

### *4.6. Alder-Ene/Cross-Coupling*

The intermolecular Alder-ene reaction of benzyldimethylsilylalkynes, catalyzed by 10 mol % of $CpRu(CH_3CN)_3PF_6$, provides trisubstituted vinylsilanes in good yields and regioselectivities. These benzyldimethylsilyl-substituted alkenes can then be further functionalized through palladium-catalyzed cross-coupling with aryl iodides or bromides in the presence of 2.2 equiv of TBAF and 2.5 mol % of $Pd_2(dba)_3$•$CHCl_3$ in THF at 25 or 50 °C (**Scheme 5**).[21] Both the Alder-ene and cross-coupling reactions proceed efficiently to provide highly functionalized alkenes in good yields.

## 5. Summary and Outlook

The scope and generality of synthetic applications for which organosilanes can be employed in palladium-catalyzed cross-coupling reactions have grown substantially in the past five years. Nonetheless, the palladium-catalyzed cross-coupling of organosilanes with organic halides and pseudohalides is still an evolving field. Some of the major challenges that appear on the horizon are the development of (1) new, more reactive and more functional-group-tolerant organosilicon species, (2) new methods for activation of the cross-coupling process, (3) new methods for the introduction of organosilicon moieties into cross-coupling precursors, and (4) a better understanding of the mechanistic details[4,17,26c] of the activation and transmetalation steps in the process. Ongoing and future studies are certain to broaden the potential of these reactions and their applications in complex-molecule synthesis. We are confident that the burst in activity in this area over the past few years will continue unabated, and bring with it new and exciting advances in organosilicon chemistry.

## 6. Acknowledgements

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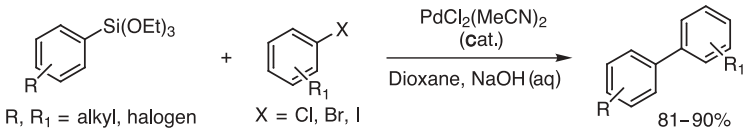
## About the Authors

Scott E. Denmark was born in Lynbrook, NY, on June 17, 1953. He obtained an S.B. degree from MIT in 1975 (working with Richard H. Holm and Daniel S. Kemp) and his D.Sc.Tech. (under the direction of Albert Eschenmoser) from the ETH Zürich in 1980. That same year, he began his career at the University of Illinois. He was promoted to associate professor in 1986, to full professor in 1987 and, since 1991, he has been the Reynold C. Fuson Professor of Chemistry. His research interests include the invention of new synthetic reactions, exploratory organoelement chemistry, and the origin of stereocontrol in fundamental carbon–carbon-bond-forming processes. Professor Denmark is currently on the Board of Editors of *Organic Reactions* and *Organic Syntheses.* He is Associate Editor of *Organic Letters* and Editor of *Topics in Stereochemistry.*

Michael Ober was born in Belleville, MI, on July 30, 1977. He graduated from Rose-Hulman Institute of Technology in 1999 with a B.S. degree in chemistry and minor degrees in chemical engineering and philosophy. He is currently a graduate student at the University of Illinois, working under the guidance of Professor Scott E. Denmark.

# New Alkoxysilanes

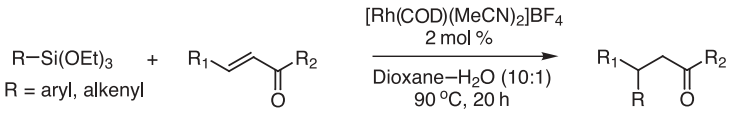
**The use** of silicon compounds as transmetalation reagents has attracted much attention as a viable alternative to the popular Stille and Suzuki coupling reactions, mainly due to the formation of nontoxic byproducts and the stability of the reagents to many reaction conditions.[1] Silicon-based coupling reactions can be carried out using aryl, heteroaryl, or alkenyl halides and alkoxysilanes in the presence of palladium or rhodium catalysts. Among the various types of silicon compounds available, alkoxysilanes are most effective in the coupling reactions.



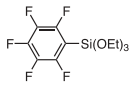

R, $R_1$ = alkyl, halogen

X = Cl, Br, I

**Recently,** considerable attention has been paid to the rhodium-catalyzed addition of aryl(trialkoxy)silanes to carbonyl compounds, such as aldehydes, α,β-unsaturated ketones and esters.[2]




**59,275-7**

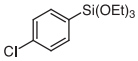



5g
10g
25g

**17,556-0**

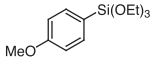

100mL
500mL

**59,791-0**



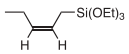

1g
10g

**59,701-5**



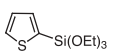

5g
20g

**59,264-1**



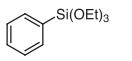

1g
5g

**59,700-7**



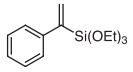

1g
10g

**17,560-9**



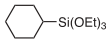

5g
250g
1kg

**59,635-3**



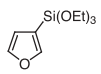

1g
10g

**59,242-0**



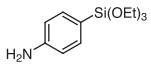

1g
5g

**59,231-5**



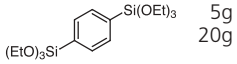

5g

**59,647-7**



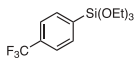

1g
10g

**59,803-8**



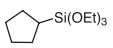

5g
20g

**63,043-8**



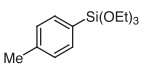

1g
5g

**59,604-3**



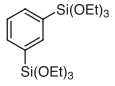

5g

**59,157-2**




1g
5g

**59,813-5**




1g
10g

**22,565-7** Bis(acetonitrile)dichloropalladium(II), 99%

$PdCl_2(MeCN)_2$

500mg
5g

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**References:** (1) For a review, see the preceding article in this issue: Denmark, S. E.; Ober, M. H. *Aldrichimica Acta* **2003**, *36*, 75. (2) Oi, S. et al. *Org. Lett.* **2002**, *4*, 667.

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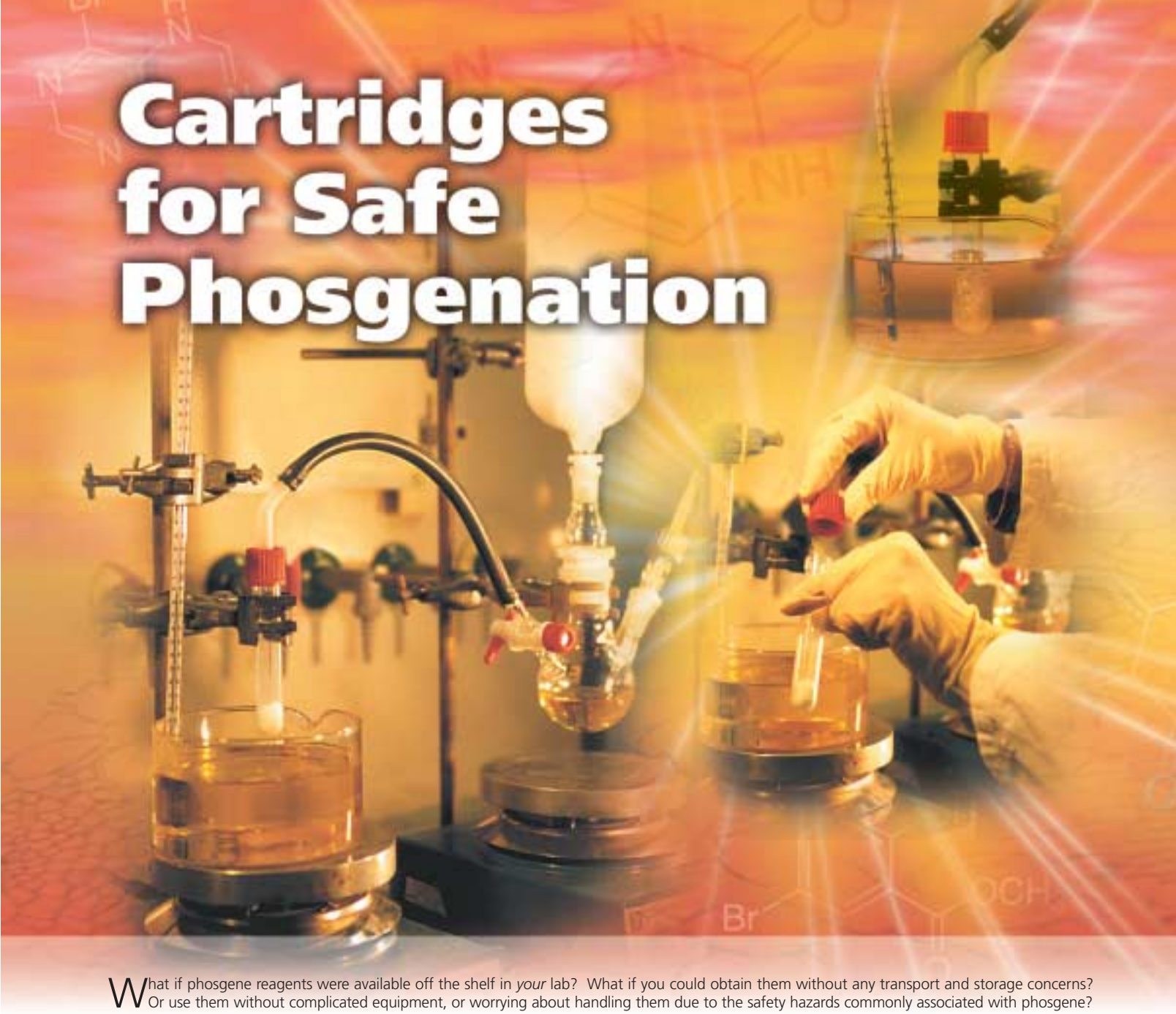

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- Suitable for magnetic stirring.
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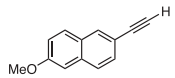
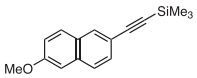
**63,263-5**

$C_{13}H_{10}O$ 182.22 — 1g, 5g



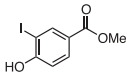
**63,335-6**

$C_{16}H_{18}OSi$ 254.41 — 1g, 5g



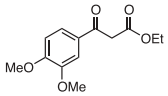
**63,194-9**

$C_8H_7IO_3$ 278.05 — 1g, 5g



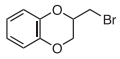
**59,316-8**

$C_{13}H_{16}O_5$ 252.27 — 1g, 5g



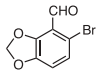
**63,264-3**

$C_9H_9BrO_2$ 229.07 — 1g, 5g



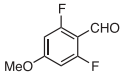
**59,737-6**

$C_8H_5BrO_3$ 229.03 — 1g, 5g



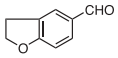
**63,180-9**

$C_8H_6F_2O_2$ 172.13 — 1g, 5g



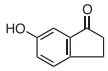
**63,195-7**

$C_9H_8O_2$ 148.16 — 1g, 5g



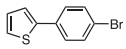
**63,454-9**

$C_9H_8O_2$ 148.16 — 5g



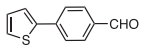
**59,666-3**

$C_{10}H_7BrS$ 239.13 — 1g



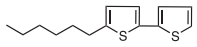
**59,732-5**

$C_{11}H_8OS$ 188.25 — 1g



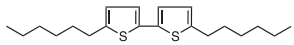
**63,051-9**

$C_{14}H_{18}S_2$ 250.43 — 500mg, 1g



**63,295-3**

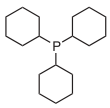
$C_{20}H_{30}S_2$ 334.59 — 1g, 5g



## *New Reagents*

**59,228-5**

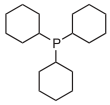
$C_{18}H_{33}P$ 280.44 — 100mL



Tricyclohexylphosphine
1M solution in toluene

**59,239-0**

$C_{18}H_{33}P$ 280.44 — 100mL



Tricyclohexylphosphine
1M solution in THF

**59,370-2**

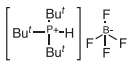
$H_4AlLi$ 37.95 — 25mL, 100mL

$LiAlH_4$

Lithium
aluminum hydride
**2.0M solution in THF**

**57,894-0**

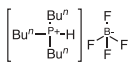
$C_{12}H_{28}BF_4P$ 290.13 — 1g, 5g



Tri-*tert*-butylphosphine
tetrafluoroborate

**57,649-2**

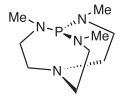
$C_{12}H_{28}BF_4P$ 290.13 — 1g, 5g



Tri-*n*-butylphosphine
tetrafluoroborate

**46,355-8**

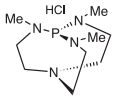
$C_9H_{21}N_4P$ 216.27 — 1g, 5g



*N*-Methyl Superbase

**59,815-1**

$C_9H_{22}ClN_4P$ 252.73 — 1g, 5g

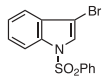


*N*-Methyl Superbase
hydrochloride

## Heterocyclic Building Blocks

**63,393-3**

$C_{14}H_{10}BrNO_2S$ — 1g
336.21 — 10g

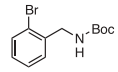


**47,996-9**

$C_5H_4N_4$ — 1g
120.11 — 5g

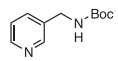
**63,406-9**

$C_{12}H_{16}BrNO_2$ — 1g
286.17



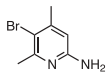
**63,444-1**

$C_{11}H_{16}N_2O_2$ — 1g
208.26 — 5g



**63,420-4**

$C_7H_9BrN_2$ — 1g
201.07 — 5g



**63,215-5**

$C_6H_4ClNO$ — 1g
141.56 — 5g

**63,276-7**

$C_7H_7NO_3$ — 1g
153.14 — 5g

**63,214-7**

$C_6H_4BrNO$ — 1g
186.01 — 5g

**63,246-5**

$C_6H_4BrNO_2$ — 1g
202.01 — 5g

**63,341-0**

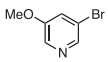
$C_6H_4ClNO_2$ — 1g
157.56 — 5g

**59,317-6**

$C_6H_4FNO_2$ — 1g
141.10 — 5g

**63,181-7**

$C_6H_6BrNO$ — 1g
188.02 — 5g



## Versatile Boronic Esters

**56,814-7**

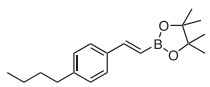
$C_{10}H_{21}BO_2$ — 1g
184.08 — 5g

**63,334-8**

$C_8H_{15}BO_2$ — 1g
154.02 — 10g

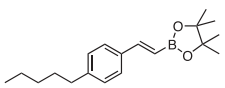
**59,287-0**

$C_{18}H_{27}BO_2$ — 1g
286.23 — 5g



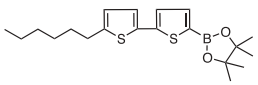
**59,298-6**

$C_{19}H_{29}BO_2$ — 5g
300.25 — 25g



**63,296-1**

$C_{20}H_{29}BO_2S_2$ — 1g
376.39 — 5g



**63,156-6**

$C_8H_{10}BNO_2$ — 1g
162.99 — 5g

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# 2003 Young Chemist in Industry Awards

Sigma-Aldrich is pleased to announce the winners of the *Young Chemist in Industry* awards, presented on April 30, 2003 at the 12th Young Chemists Meeting in London.

This annual, one-day meeting showcases organic chemistry research undertaken in an industrial setting by chemists under the age of 30 who do not hold a Ph.D. It represents a unique opportunity for younger chemists to present their research to an industry-wide audience. This year's gathering was attended by over 85 young scientists and featured 10 presentations by participants, and a guest lecture by Dr. Dave Tapokzay.

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

***First Prize:***

**Amanda Boase**, *Merck, Sharp & Dohme (Harlow)*
GABA-A a5-Subtype Selective Inverse Agonists as Potential Cognition-Enhancing Agents

***Second Prize:***

**James Peace**, *Syngenta (Bracknell)*
Discovery of the Cyanotropanes, a Novel Class of Insecticides

***Third Prize:***

**Colin Gray**, *Organon (Newhouse)*
Web Based Chemoinformatics: Making the Drug Discovery Process More Efficient

*Front row (left to right):* Julia Lainton (Scientific Organizer), David Walker, Helen Feilden, Cedric Poinsard, and David Proctor (Scientific Organizer). *Back row (left to right):* Frederic Cordier, James Peace, Alex Smith (Scientific Organizer), Colin Gray, Peter Barton, and Robert Sheppard.

# Cross Metathesis of Nitrogen-Containing Systems

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## Outline



## 1. Introduction

Olefin metathesis is now firmly established as an important and general reaction in synthetic organic chemistry. One variant, known as cross metathesis (CM), uses a transition metal to catalyze the exchange of alkylidene groups on two independent alkenes to give a new, differently substituted alkene. The first reports of CM featured the coupling of allyl methyl sulfide with unfunctionalized alkenes using a tungsten–carbene complex,[1] and the use of Schrock's catalyst (**1**) in the cross metathesis of styrene.[2] Cross metathesis has since evolved into a highly practical synthetic tool, owing to the availability of advanced catalysts that provide excellent functional-group tolerance and the ability to conduct reactions under mild conditions.

A number of other types of metathesis reactions are known, including ring-closing, domino, ring-opening, ring-expansion, and polymerization metatheses. However, this review focuses on the cross metathesis of nitrogen-containing alkenes and alkynes, many of which are of biological significance. The review begins with a survey of the catalysts that are currently available for metathesis chemistry. Those catalysts that are most suited to cross metathesis are identified, as are practical considerations that need to be taken into account when carrying out these reactions. A number of other reviews have been written over the past few years in the area of metathesis chemistry: general reports,[3–7] the application of metathesis to carbohydrate chemistry,[8,9] sequential metathesis,[10] the ring-closing metathesis of nitrogen-containing compounds,[11] and a review of ruthenium complexes as metathesis catalysts.[12]

## 2. Catalysts

Numerous catalysts are available to facilitate metathesis reactions. However, only a few are used on a regular basis (**Figures 1** and **2**). The complexes shown in these two figures have alternately been called "precatalysts", "initiators", or "promoters" in the literature. To simplify the discussion in the rest of the review, complexes **1–24** will be called catalysts, with the understanding that they often are the precursors of the active catalytic species, which is formed by dissociation of a suitable ligand from **1–24**. Schrock's molybdenum–alkylidene catalyst (**1**), one of the first metathesis catalysts to be developed,[13] is known to tolerate β-lactam[14] and acrylonitrile functionalities, but is not compatible with unprotected amines, free alcohols, acetate groups, enones, and enoic esters. Despite these drawbacks, commercially available **1** is highly reactive toward a range of substrates that contain a variety of functional groups. In general, Schrock's catalyst gives shorter reaction times and higher yields than the more widely used ruthenium catalysts such as **9**. However, the general use of **1** remains somewhat problematic due to its sensitivity toward atmospheric oxygen. There are a number of other molybdenum catalysts available (see Figure 1); for example, chiral carbenes **2**[15]

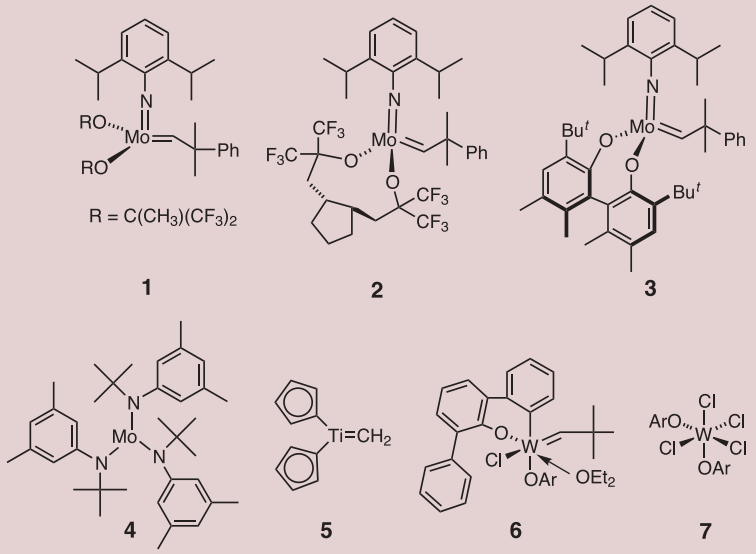



**Figure 1**. Molybdenum, Tungsten, and Titanium Metathesis Catalysts.

and **3**,[16] and achiral carbene **4**,[17] the latter of which is activated in situ by dichloromethane. Catalyst **4** has found use in the cross metathesis of alkynes that contain both electron-donating and electron-withdrawing substituents, and where tolerance of polar groups such as ethers, esters, nitriles, acetals, sulfones, and silyl ethers is required.[17]

Complex **8**, one of the first ruthenium–carbene catalysts reported,[18] effects the ring-closing metathesis (RCM) of suitably substituted precursors, leading to conformationally constrained amino acids and peptides.[19] However, its use has been somewhat superceded by what remains one of the most commonly used metathesis catalysts—Grubbs "first generation" catalyst, **9**.[20] Commercially available **9** initiates metathesis reactions more rapidly than the earlier catalyst **8**, and tolerates functionalities such as carbamate hydrogens,[21] unprotected carboxylic acids,[22] and a wide range of peptide protecting groups,[21] while remaining relatively air- and moisture-stable. Despite its widespread applications in metathesis reactions, catalyst **9** does have some drawbacks such as sluggish reactivity especially in the cross metathesis of unprotected homoallylic alcohols and allyltrimethylsilane,[23] and of substituted double bonds.[24] The bimetallic catalyst **10** was recently reported to have a catalytic activity that is similar to that of **9**, but with the advantage of increased stability, ease of storage, and the ability to be recovered and recycled.[25]

Water-soluble ruthenium catalysts such as **11** and **12** have been developed to allow metathesis reactions to be carried out in polar solvents, a feature that is particularly important if biological applications involving water-soluble substrates are to be fully realized. These catalysts, synthesized by a ligand-exchange reaction of catalyst **9**, show good RCM activity in solvents such as water and methanol.[26] Catalysts **11** and **12** have, however, found limited use to date due to their high air sensitivity in solution, decomposing rapidly to form a bright green solution in the presence of trace levels of oxygen. It is interesting to note that, while catalyst **12** is also soluble in dichloromethane, it does not show activity due to its rapid decomposition in this solvent.[27] A number of other ruthenium-based catalysts have also been developed, including the infrequently used photoinducible dimer **13**[28] and the chiral benzimidazolidene catalyst **15** that has an activity comparable to that of **9**.[29]

Hoveyda reported the first recyclable ruthenium-based catalyst, **14**. This complex can be purified in high yield by silica gel column chromatography for reuse.[30] However, while **14** is comparable to **9** in its catalytic activity, it is only reactive toward terminal alkenes. Other catalysts (e.g., **20**), that exhibit improved initiation rates as compared to **14**, have also been developed.[31]

The emergence in 1999 of the now commercially available Grubbs "second generation" catalyst, **16**, proved to be a particularly significant advance in metathesis chemistry.[32] The steric bulk and increased basicity of the dihydroimidazolidene ligand in **16** and **17** impart improved stability and activity as compared to the "first generation" catalyst **9**.[33] Catalyst **16**, which has a similar, if not improved, functional-group tolerance with respect to **9**, has been used to prepare functionalized trisubstituted double bonds by cross metathesis.[34] Catalyst **16** has found use in cross-metathesis reactions involving α,β-unsaturated esters, ketones, aldehydes, and a variety of other groups as detailed in this review.[35]

A "second generation recoverable", phosphine-free catalyst, **17,** has been developed by Hoveyda and co-workers.[36] This catalyst is highly reactive, recyclable via silica gel based chromatography, and extremely stable when exposed to water and/or air. Although not widely available commercially, its preparation has been published and its crystal structure determined. Catalyst **17** is very effective in cross-metathesis reactions, where one olefin is electron-deficient. For example, highly selective cross metathesis of α,β-unsaturated nitriles and acrylonitriles has been achieved using **17** but not **16**. Also, in contrast to **16**, catalyst **17** is reasonably soluble in methanol at room temperature and readily soluble at 50 °C; however, it remains completely inactive in water-based solvent systems.[37] In addition, catalyst **17** is compatible with unprotected alcohol[38a] and acid[33] groups, and has been used to synthesize unsymmetrical, functionalized, disubstituted olefins with good stereoselectivity under mild conditions.[38a] A variety of functionalities are tolerated including base-sensitive groups, and as such cross metathesis can be used to replace Wittig or Horner–Wittig reactions where substrates are base-sensitive. The dendrimeric **24** has been reported as an alternative to **17**, with an improved ability to be recycled by silica gel filtration.[36]

A variety of solid-phase catalysts related to **17** have also been reported, including **21**, **22**, and **23**. Deep-green resin **22**, synthesized from **16** and immobilized onto Wang resin, is a particularly stable and recyclable catalyst that shows good cross-metathesis activity even with highly electron-deficient olefins.[39] Solid-supported **21** shows high ring-closing metathesis activity, but much lower cross-metathesis activity as compared to **22**. Catalyst **23** has been used for cross-metathesis reactions in methanol or water in ambient air.[37]

Blechert and co-workers reported the novel ruthenium–alkylidene catalysts **18** and BINOL-based **19** as an addition to

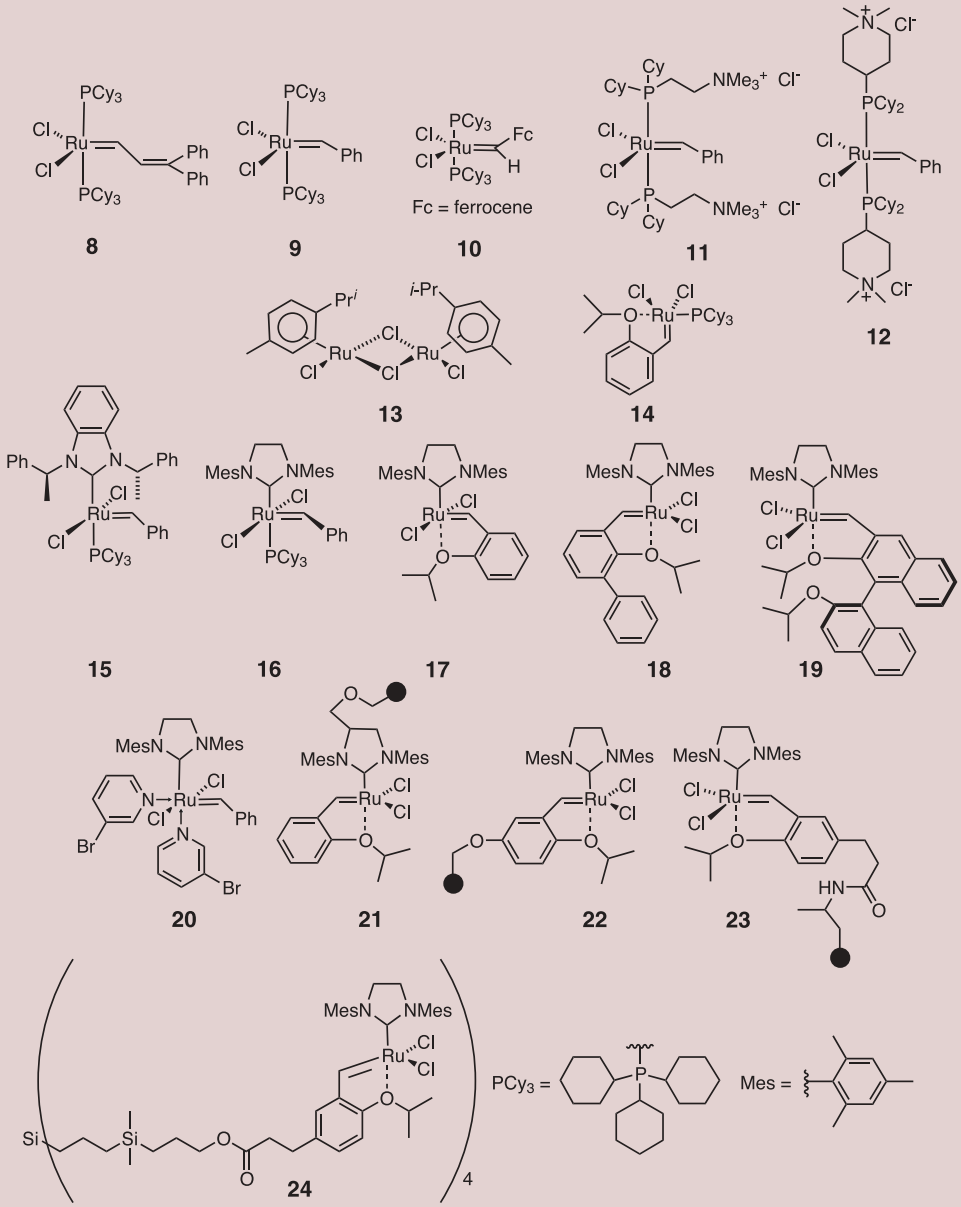



**Figure 2**. Ruthenium Metathesis Catalysts.

the growing list of second-generation catalysts.[40,41] These catalysts are significant in that they display increased activity, relative to **16** and **17**, while retaining stability even after exposure to air for one week. The improved reactivity and stability of these catalysts has been attributed to the increased steric bulk of the ligands.

Metals other than molybdenum and ruthenium can also form the basis of metathesis catalysts (see Figure 1). For example the titanium carbene **5**[42] and the tungsten catalysts **6** and **7** have found use in cross-metathesis reactions.[1,43]

## 3. Catalysis Mechanism

The generation of metallacyclobutane intermediates by alternating [2+2] cycloadditions and cycloreversions is the generally accepted mechanism for the cross metathesis of alkenes and alkynes.[44] A simplistic version of this, the so-called "Chauvin mechanism", is depicted in **Figure 3**. The choice of olefin that initially binds to the catalyst (step **A**) is dependent upon a variety of issues related to the electronic and steric properties of the alkene or alkyne.[45,46]

The key steps in the catalytic cycle are as follows: The cycle is initiated by coordination of an alkene to the ruthenium metal (step **A**) to form what has been termed a "ruthenacycle," which fragments rapidly (step **B**) to give a newly substituted alkylidene with the release of ethylene gas. A second alkene then reacts regio- and stereoselectively with this alkylidene (step **C**) to give a second metallacyclobutane (steps **D** or **D1**). The formation of the metalla ring shown in step **D** is highly favored over that in **D1**.[47] The favored metallacycle breaks down to regenerate the

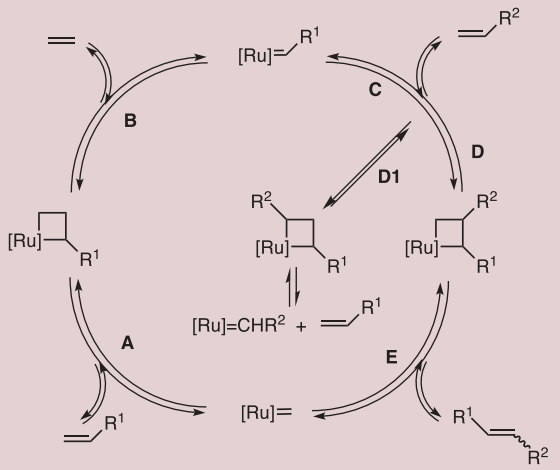



**Figure 3**. Schematic Representation of the Cross-Metathesis Mechanism.

active catalytic species and the desired cross-metathesis product (step **E**). It should be noted that phosphine-based catalysts coordinate to the alkene only after an initial pre-equilibrium dissociation of a $PCy_3$ group.[12,20,45]

Catalyst activity is directly related to the electron-donating ability of the phosphine ligands: σ donation of the phosphine ligands stabilizes the fourteen-electron metallacyclobutane intermediate; while the larger and the more strongly electron-donating the halide ligands (I<<Br<Cl) are, the lower the catalytic activity.[12] Catalytic activity also depends on catalyst initiation (related to the nature of the alkylidene moiety) and catalyst lifetime (decomposition rate of catalyst).

## 4. Reaction Scope and Conditions

While a variety of reaction conditions have been employed in metathesis chemistry, there are some standard techniques that generally improve reaction yields. A number of the factors that are known to influence the outcome of cross-metathesis reactions are discussed in this section.

The efficiency of formation of coupled alkene products in cross-metathesis reactions can be facilitated by removing the byproduct, ethylene, formed during the course of the reaction. For example, the conversion of vinylsilanes into cross-metathesis products is quantitative when ethylene is removed using a gentle stream of argon. In contrast, yields decrease considerably to around 20% in the absence of purging.[47] This simple procedure should be adopted in all cross-metathesis reactions. Where the substrates have a low viscosity, a static vacuum can be used to remove ethylene.[5]

There seems to be no advantage in using argon rather than nitrogen[22] in cross-metathesis reactions involving ruthenium-based carbene catalysts, or by working in a dry box rather than using Schlenk techniques for reactions involving common catalysts such as **9** and **16**.[21] However, the yield of the cross-coupled product can, in general, be improved by increasing the number of equivalents of one terminal alkene coupling partner (up to four equivalents). It has also been shown that the most effective molarity range of second-generation Grubbs catalyst **16** is 5–20 mol %. Lower levels of **16** generally result in sluggish reaction with very low yields of product, while higher levels tend to give rise to side products in which the benzylidene group from the catalyst is transferred to the alkene substrate.[48]

The most commonly used solvents in metathesis reactions are dichloromethane, carbon tetrachloride, benzene, or 1,2-dichloroethane at reflux or at room temperature. It is important to note that **16** is more thermally stable than **9**, such that reactions at reflux are best carried out using the former complex. The use of reflux conditions has the added advantage of better facilitating the removal of ethylene from the reaction.

Isolation of Grubbs ruthenium catalysts **9** and **16** from reaction mixtures is often difficult due to the presence of residual ruthenium byproducts and, as such, a number of experimental techniques have been developed to aid catalyst removal and subsequent purification. Georg and co-workers developed an effective method for removing catalyst **9** from crude ring-closing-metathesis reaction mixtures. Here, the crude product is stirred with triphenylphosphine oxide or dimethyl sulfoxide, and the resulting complex is removed by filtration through silica gel.[49a] Maynard and Grubbs also reported a method in which residual ruthenium byproducts from **9** are removed as water-soluble ruthenium–tris(hydroxymethyl)-phosphine complexes.[50] However, this method has the drawback that many equivalents of the expensive phosphine ligand are required. Residual ruthenium from catalyst **9** and other highly colored impurities have been effectively removed from crude reaction mixtures by oxidation with a small amount of $Pb(OAc)_4$ followed by filtration through a silica plug.[51] These experimental techniques for the removal of residual ruthenium from the crude reaction mixture have become somewhat redundant with the development of recyclable catalysts such as **17**, which can be separated from reaction mixtures by silica gel based chromatography and subsequently recycled for future use.

## 5. Cross Metathesis with Alkenes

Cross-metathesis reactions of alkenes have been carried out on a range of substrates, many of which contain nitrogen, an element that is often associated with biological activity. In the following sections, we have divided these examples of nitrogen-containing substrates into a number of useful and functional groupings.

### *5.1. Amino Acids and Peptides*

The application of cross-metathesis methodology to amino acids and peptides has attracted considerable attention as a means to prepare modified amino acids and peptidomimetics that possess useful chemical and biological properties. A number of variants of cross metathesis have been reported, which differ in the point of attachment of the alkene to the amino acid participant in the metathesis reaction. For example, a substituent bearing a terminal double bond can be attached at either the (i) α carbon, (ii) amino acid side chain, (iii) amino terminus, or (iv) carboxyl end of an amino acid. Reactions can be further classified on the basis of the parent amino acid, e.g., glycine, tyrosine, and serine.

#### *5.1.1. α-Carbon-Substituted*

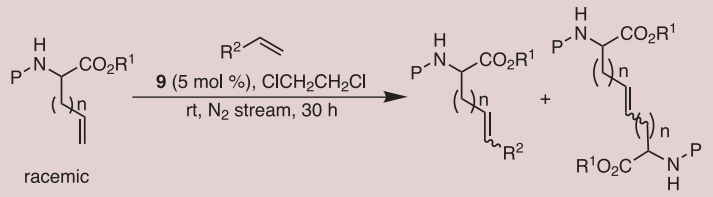
Modified glycine has proven to be a popular scaffold for cross-metathesis

chemistry. In 1997, Gibson and co-workers published the first examples of cross metathesis using protected amino acids.[22] This was followed soon after by further systematic studies (**eq 1**).[21] A variety of solvents, temperatures, reaction times, catalyst loadings, and substrate concentrations were investigated, as well as the effect of changing from a static pressure to a steady flow of nitrogen. In general, optimum conditions were achieved using a 0.25 M solution of amino acid substrate in 1,2-dichloroethane with two equivalents of styrene, 5 mol % of Grubbs first-generation catalyst **9** at room temperature, and with a steady flow of nitrogen for thirty hours. In all cases, both cross-coupled products and homodimers were isolated.

The outcome of these reactions seems to be relatively independent of the nature of the amine protection. The nature of the *C*-terminal group also seems to be relatively unimportant with methyl, benzyl, and *tert*-butyl esters giving similar results. A free acid also proved to be a suitable substrate, and homoallylglycine was generally more reactive than allylglycine.[21] However, vinylglycine does not undergo efficient cross metathesis, presumably due to the steric inaccessibility of the double bond to the catalyst. These findings illustrate the importance of the length of the alkene tether to the efficiency of cross-metathesis reactions. The applicability of this methodology to the solid phase has also been investigated using Wang resin.[21] Here, initial attempts at cross metathesis gave mixtures of cross-metathesis and self-metathesis products in relatively equal amounts, due to the lack of site isolation on the resin. It was subsequently found that "capping" the Wang resin allowed preparation of the desired cross-metathesis product in good yield.

Heterocycles have been successfully coupled to glycine derivatives. For example, racemic methyl *N*-acetylallylglycinate was coupled to 2,8-diallyldibenzothiophene as a key step in the production of antibiotic agents.[52] Two dibenzothiophene cross-metathesis products, the amino ester and the bis(amino ester), were isolated, along with two homodimeric products including a novel dibenzothiophenophane.

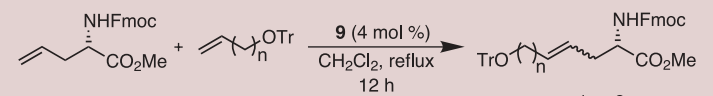
Cross-metathesis reactions have been employed by Blechert and co-workers as a preliminary step in developing a method for the catalytic cyclization and cleavage of tetrapeptide-derived macrocycles from solid supports.[53] Here, the side chain of Fmoc-allylglycine methyl ester was selectively coupled to *O*-trityl-protected alkenols of




| n | P | $R^1$ | $R^2$ | Yield, % Cross Metathesis | Yield, % Self-Metathesis |
|---|---|---|---|---|---|
| 0 | Boc | Me | Hex | 7 | – |
| 1 | Boc | Bu$^t$ | Hex | 49 | 16 |
| 1 | Boc | Me | Hex | 45 | 17 |
| 1 | Boc | Me | Ph | 15 | 21 |
| 2 | Boc | Me | Hex | 66 | 28 |
| 2 | Ac | Me | Ph | 43 | 48 |
| 2 | Boc | Me | Ph | 52 | 40 |
| 2 | Boc | Bn | Ph | 53 | 44 |
| 2 | Fmoc | Me | Hex | 58 | 25 |
| 2 | Fmoc | H | Hex | 58 | 18 |
| 2 | Phth | Me | Ph | 55 | 35 |

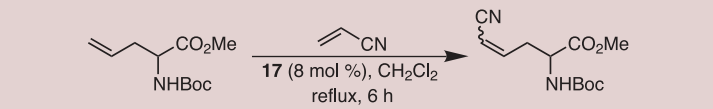
*Ref. 21*

**eq 1**




*Ref. 53*

**eq 2**




*Ref. 33*

**eq 3**

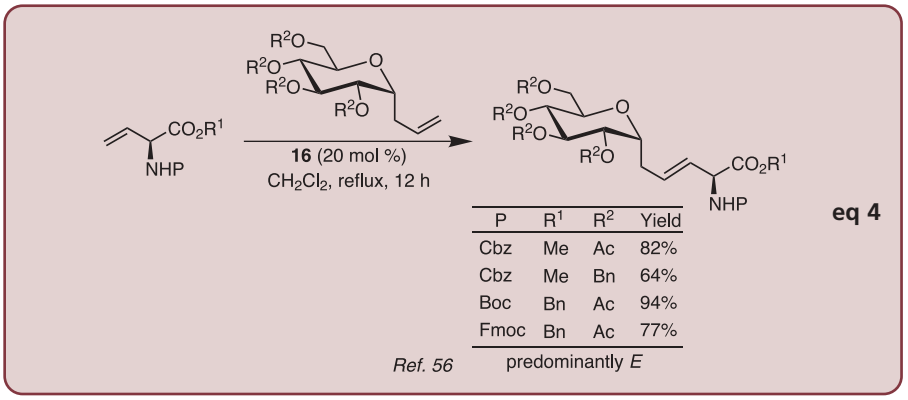
differing chain lengths, to give cross-metathesis products that were deprotected, resin-linked, and subsequently incorporated into tetrapeptides (**eq 2**).

The application of cross metathesis to allylsilanes has been developed as a basis for subsequent side-chain elaboration via the silyl group. In one example, a protected glycine derivative was functionalized using allyltrimethylsilane in excellent yield and with good stereoselectivity.[54] More recently, Blechert and co-workers utilized second-generation catalyst **17** for a highly selective cross metathesis between acrylonitriles and protected amino acids—reactions that could previously only be achieved using sensitive molybdenum catalysts (**eq 3**).[33] Again, this allows for subsequent side-chain modification.

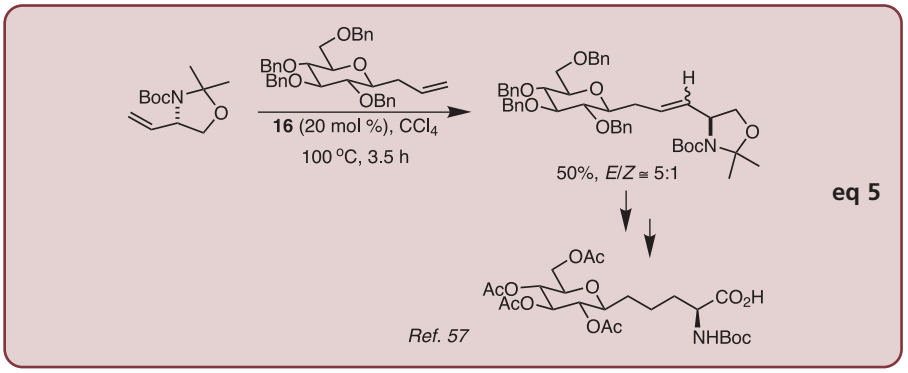
Roy and co-workers carried out the cross metathesis of a protected homoallylamine and a protected glycine derivative with suitably substituted monosaccharides to give *C*-linked carbohydrates that possess enhanced stability towards enzymatic and metabolic cleavage.[55] Reactions of this type provide convenient access to important glycopeptidomimetics, where the parent glycopeptides are known to play an important role in a number of important biological processes including tumor metastasis and chemotaxis.

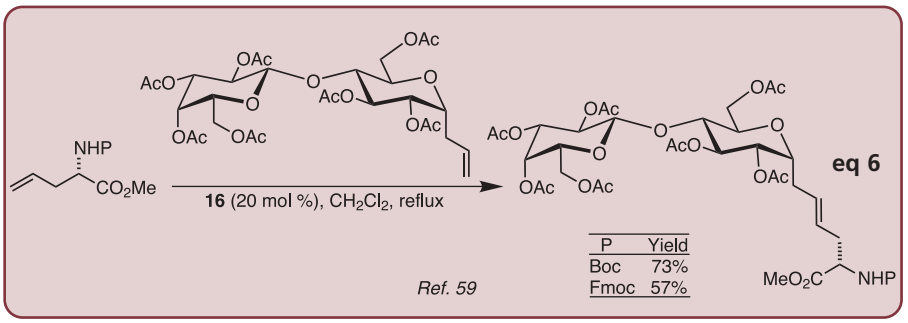
Nolen and colleagues reported related work using Grubbs second-generation catalyst **16** to give improved overall yields of *C*-glycosyl amino acids (**eq 4**).[56] Here, cross metathesis of a tetra-*O*-protected-glucose with a vinylglycine derivative proceeded efficiently, and the products obtained were hydrogenated to give *C*-glycosyl asparagines for use in enzyme assays. *C*-Glycosyl amino acids have also been prepared by reaction of *N*-Boc-vinyloxazolidine, a vinylglycine equivalent, and a sugar using Grubbs second-generation catalyst **16**; **9** does not catalyze these reactions (**eq 5**).[57] The resulting metathesis products were hydrogenated, acylated, and the oxazolidine ring oxidatively cleaved to afford a versatile building block for the synthesis of modified glycopeptides.

In a related study, Danishefsky and co-workers developed a mild and efficient

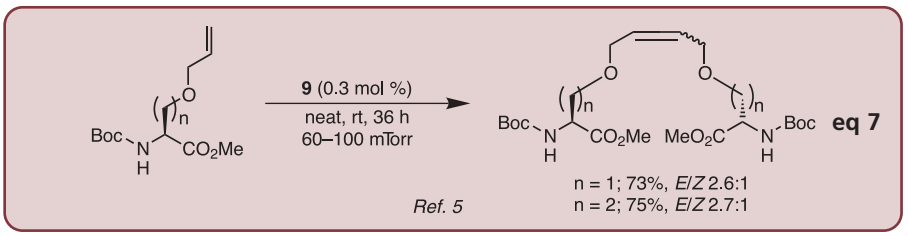



| P | $R^1$ | $R^2$ | Yield |
|---|---|---|---|
| Cbz | Me | Ac | 82% |
| Cbz | Me | Bn | 64% |
| Boc | Bn | Ac | 94% |
| Fmoc | Bn | Ac | 77% |




| P | Yield |
|---|---|
| Boc | 73% |
| Fmoc | 57% |




cross-metathesis synthesis of a hexasaccharide glycosyl amino acid that was suitable for incorporation into polymeric antitumor vaccines.[58] Here, Fmoc-L-allylglycine benzyl ester was coupled to a range of *O*-allyl glycosides to give the desired cross-metathesis products in good yields.

Other reports on the synthesis of stable glycopeptide analogues using cross-metathesis methodology have appeared with a view to identify potential therapeutic agents.[59] For example, protected *C*-allyl-glycosides have been coupled to protected allylglycine using second-generation Grubbs catalyst **16**—introduced in two equal portions at 24-hour intervals—to give moderate-to-good overall yields of coupled products. Both Boc and Fmoc protecting groups seem to function equally well in these reactions. This initial work was extended to allow the conjugation of *C*-allyllactose as a first step in the development of a co-translational glycopeptide synthetic strategy (**eq 6**).[59]

The amino acid serine has also been used as a basis for developing cross-metathesis methodologies. For example, Grubbs and colleagues explored a number of cross-metathesis reactions of serine derivatives with both terminal and substituted alkene coupling partners.[5] Allyl ethers of protected serine residues were dimerized by cross metathesis under reduced pressure (**eq 7**), while treatment of Boc-L-serine(*O*-allyl) methyl ester with bis(9-nonenyl acetate), itself made by cross metathesis, generated a lipophilic amino acid in high yield and with good stereoselectivity.[5] Larger and more complex architectures also appear to be compatible with cross-metathesis chemistry. For example, a hydrophobic pentapeptide framework has been elaborated.[5] The dimerized pentapeptide represents an example of side chain to side chain cross-linking via a non-native *C–C* linkage.

Aryl-substituted *C*-fucopeptides have been synthesized using cross-metathesis methodology These products are important in that they mimic tetrasaccharide sialyl Lewis X, a carbohydrate-based terminal unit found in cell-surface glycoproteins and glycolipids, which interacts with E- and P-selectin to mediate the early stages of an inflammatory response. It was found that cross metathesis at room temperature failed to give the desired coupled products. However, reaction at reflux afforded an array of products in reasonable yields, with the electron-poor pentafluorostyrene giving the lowest yield of cross-metathesis product (**eq 8**).[60] The authors noted that activated aromatic and nonaromatic olefins gave mixtures of *E* and *Z* isomers, while nonactivated aromatic olefins produced only the *E* isomers. The final products were screened for E- and P-selectin binding.

Tyrosine-based systems have been used in cross-metathesis reactions, where the *O*-allyl tether is of sufficient length to allow cross metathesis to proceed.[5] By contrast, the analogous dimerization of Boc-L-allylglycine methyl ester does not proceed well, because the close proximity of the double bond to the amino acid backbone appears to hinder catalyst binding.

### 5.1.2. N-Substituted

There are comparatively far fewer examples of cross-metathesis reactions of an olefin attached to the α nitrogen of an amino acid or peptide. Nevertheless, cross metathesis of *N*-alkenylpeptoids and *O*-allyl glycosides has been reported by Hu and Roy to give mixtures of *E* and *Z* metathesis products (**eq 9**).[61] The reaction is tolerant of free carboxylic acids, but not of secondary amine functionalities. It was found that a shorter tether between the nitrogen and the double bond results in a lower yield of the desired cross-metathesis product.

### 5.1.3. O-Substituted

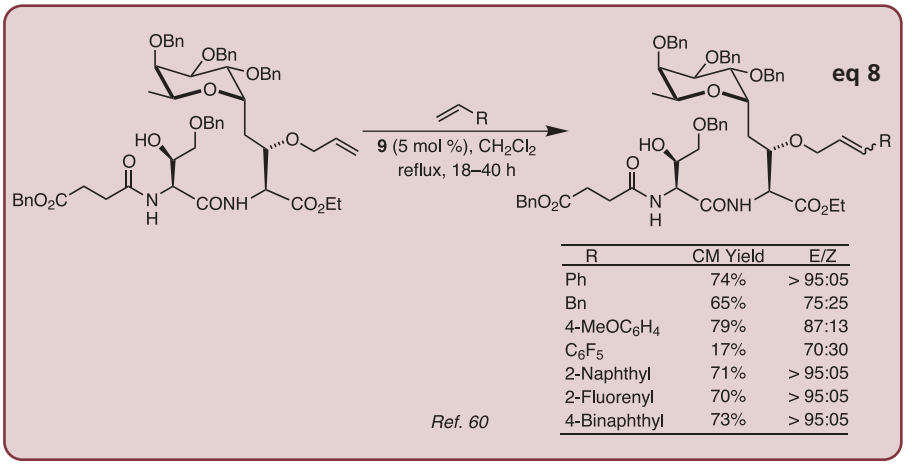
Cross metathesis at the *C* terminus of suitably substituted amino acids and peptides has also been reported. For example, 9-decen-1-yl Boc-glycinate reacts with 9-decen-1-yl acetate homodimer, in the presence of catalyst **9**, to give a differently functionalized 9-octadecene-1,18-diol (**eq 10**).[5] This glycine derivative also undergoes self-metathesis to give a novel amino acid homodimer in excellent yield.[5]

Cross-metathesis reactions of this type have also been extended to the solid phase using a polystyrene (1% DVB) resin.[62] These resin-bound amino acids and peptides can be chemically manipulated and subsequently cleaved from the resin. In another solid-phase example, Schreiber and colleagues carried out "intra-site" cross-metathesis reactions in near quantitative yields on individual polystyrene polymer beads with a silyl linker (**eq 11**),[63] and found that the alkyl chain length had little effect on the reaction efficiency. Here, the metathesis step can be viewed as a ring-closing metathesis, despite the net overall result being the same as that from a solution-phase cross metathesis.

### 5.2. Carbamates

There are numerous non-amino acid based examples of cross metathesis in which an amine nitrogen is protected by a carbamate (e.g., Cbz, Boc, and Fmoc). (The protection of an amine is especially important in cross-metathesis chemistry since most catalysts are poisoned by this functional group.) For example, carbamates have been utilized to synthesize functionalized allylsilanes using cross metathesis.[54] In addition, Fmoc-protected amines, which are potential starting materials for the synthesis of nonnatural amino acids, have been prepared by cross metathesis of an allylstannane using molybdenum catalyst **1** (**eq 12**).[64] The fact that cross-metathesis chemistry is compatible with allylstannanes is of particular significance, because allylstannanes are valuable reagents for nucleophilic additions and radical reactions.

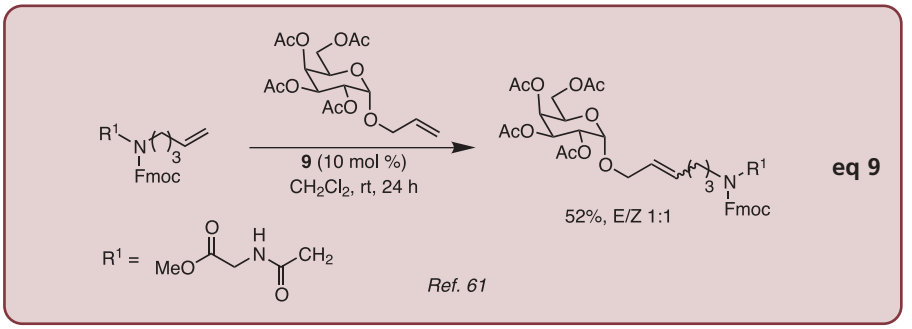
Second-generation Grubbs catalyst **16** has been used to promote the cross metathesis of a number of non-amino acid carbamates. A key step in a reported synthesis of (–)-prosophylline, a prosopis alkaloid with antibiotic and anesthetic properties, involves a cross-metathesis-based side-chain extension (**eq 13**).[65] The cross-coupling step was followed by hydrogenation and deprotection to give the final




eq 8

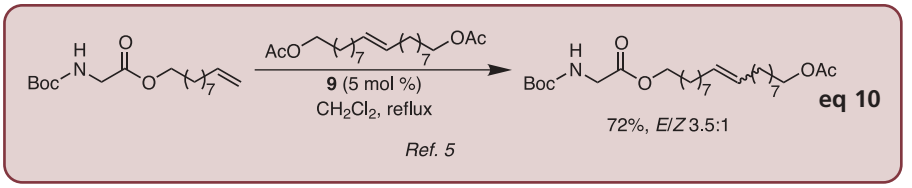
| R | CM Yield | E/Z |
|---|---|---|
| Ph | 74% | > 95:05 |
| Bn | 65% | 75:25 |
| 4-MeOC$_6$H$_4$ | 79% | 87:13 |
| C$_6$F$_5$ | 17% | 70:30 |
| 2-Naphthyl | 71% | > 95:05 |
| 2-Fluorenyl | 70% | > 95:05 |
| 4-Binaphthyl | 73% | > 95:05 |

*Ref. 60*



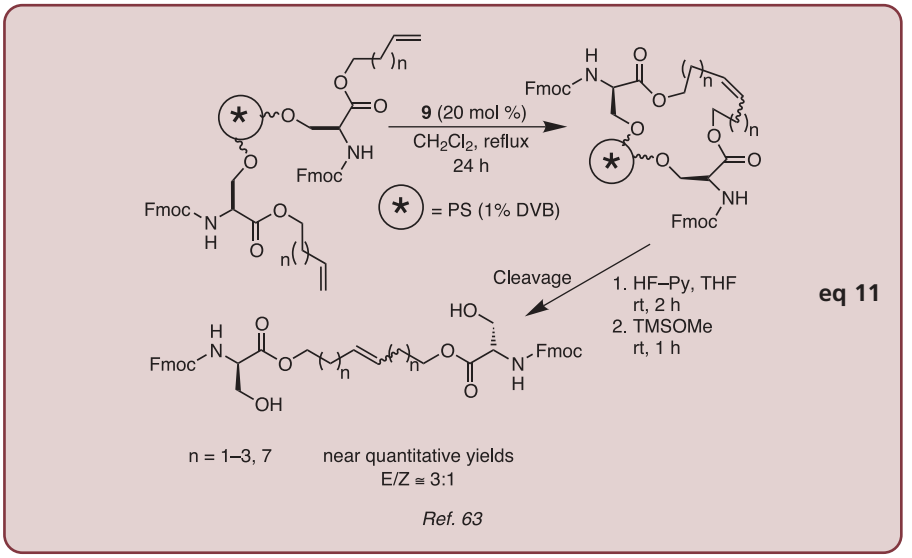

eq 9

*Ref. 61*



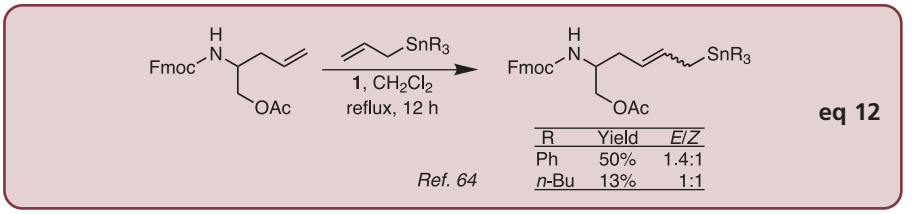

eq 10

*Ref. 5*




eq 11

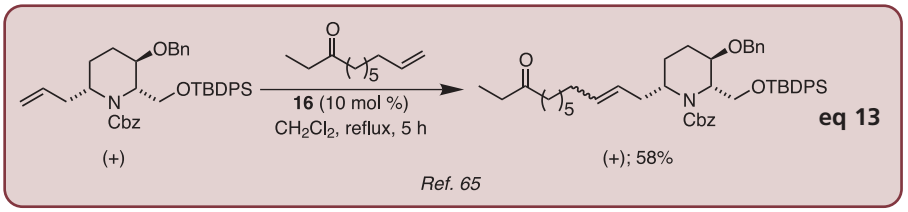
*Ref. 63*

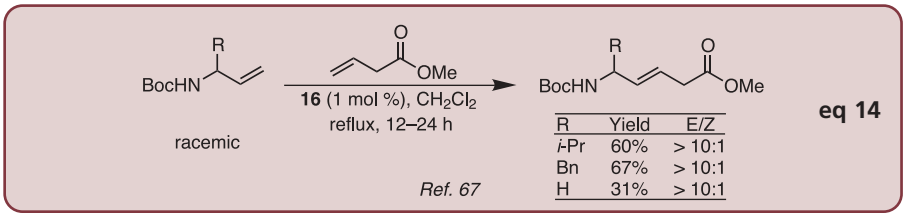


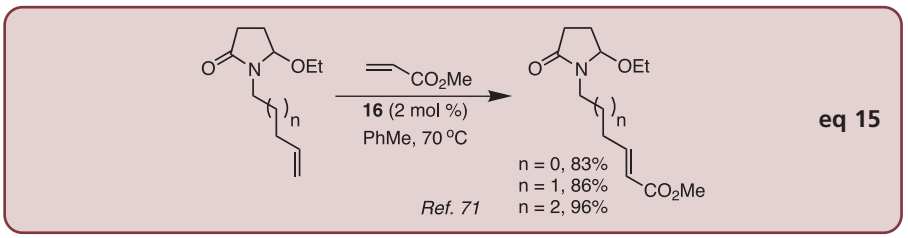

| R | Yield | *E/Z* |
|---|---|---|
| Ph | 50% | 1.4:1 |
| *n*-Bu | 13% | 1:1 |

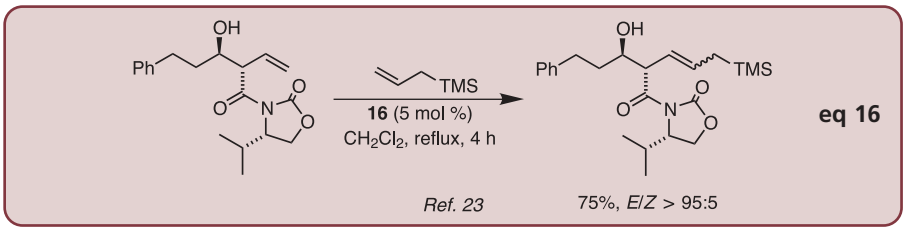
eq 12

*Ref. 64*




natural product. Roy and co-workers have also used catalyst **16** to facilitate the cross metathesis of allyl halides and terminal olefins in good yield and with excellent *E*/*Z* selectivity.[66] This sequence was extended to N-protected allylglycine to provide convenient access to useful peptidomimetics.

In an interesting piece of work, Vasbinder and Miller explored the isosteric replacement of peptide bonds using a convergent, cross-metathesis synthetic strategy.[67] The isosteric replacement of amide bonds to give β,γ-unsaturated δ-amino acids results in useful structural peptidomimetics that are less susceptible to biodegradation via proteolytic cleavage and, as such, have proved valuable in pharmaceutical drug design.[68] Allylic amines derived from either valine, phenylalanine, or glycine were coupled to methyl 3-butenoate to afford the isosteres in moderate yields (**eq 14**).[67] In another example of this methodology, a Pro-Gly dipeptide isostere was formed in 83% yield from vinyl-substituted pyrrolidine, itself prepared from Boc-protected proline methyl ester.[67]

A stereodiversified library of *trans*-1,4-enediols has been synthesized and subsequently screened for mu opioid receptor affinity. Eight enediol diastereomers were synthesized by cross metathesis in yields ranging from 51 to 81%. These were then separated into a total of sixteen stereoisomers using reverse-phase HPLC.[69]

### 5.3. Amides

Suitably substituted amides, other than those that constitute a peptide bond, have also proven to be useful substrates for cross metathesis. For example, Piva and co-workers submitted oxoamides to cross metathesis with trimethyl(allyl)silane to produce novel allylsilane derivatives.[70] Functionalized allylsilanes have also been prepared in excellent yields from chlorinated substrates containing amide linkages.[54] In addition, *N*,*O*-acetals bearing an olefinic side chain undergo cross metathesis with methyl acrylate in excellent yields—the longer the tether, the higher the yield (**eq 15**).[71]

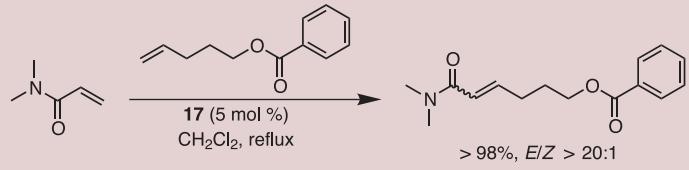
The ability to dimerize resin-bound, amide-containing olefins in good yields has been demonstrated using metathesis chemistry.[72] The initial metathesis reaction is strictly an example of ring-closing metathesis, since both coupling partners are attached to the solid support. However, the net result after cleavage from the solid support is analogous to a solution-phase cross-metathesis reaction. (This approach is similar to that depicted in equation 11 for resin-bound amino acids.)

There are a number of cross-metathesis reactions on systems that are not true amides. These reactions are included here for convenience. A key step in a recently reported enantioselective total synthesis of (+)-amphidinolide T1 involves a cross-metathesis coupling of two key fragments, in the presence of catalyst **16**, to give a 60% yield of the desired cross-metathesis product as a 1:1 mixture of *E* and *Z* isomers in addition to some alkene dimers.[73] These alkene dimers were then exposed to catalyst **16** in a second metathesis reaction, affording an additional 36% yield of the cross-metathesis product (96% overall). In a related example, a cross-metathesis reaction was carried out that gave high *E*-olefin selectivity (**eq 16**).[23] This selectivity is thought to be due to the formation of a five-membered chelate ring between the homoallylic hydroxyl group and the ruthenium in a metallacyclic intermediate, thus giving rise to kinetically controlled products highly selectively.

There are numerous examples of nitrogen-containing cross-metathesis reactions that involve α,β-unsaturated amides. Grubbs and co-workers conducted a systematic study on the cross metathesis of α,β-unsaturated amides with terminal olefins using the second-generation catalyst **16**.[74] Cross metathesis was shown to be compatible with Weinreb amides and oxazolidinone imides, both of which are widely utilized in organic synthesis. All reactions afforded products with excellent *E*/*Z* diastereoselectivities. The authors report that electron-donating substituents on the amide nitrogen, such as alkyl groups, gave lower yields, whereas electron-withdrawing groups afforded higher cross-metathesis yields. It has been suggested that the amide carbonyl group chelates to the metal center, the extent of which is dependent on the electron density at the oxygen atom.[36,74,75] The amide nitrogen substituent greatly affects the outcome of the metathesis reaction, since chelation of the amide carbonyl group to the metal center results in a decrease in catalyst turnover. This is demonstrated by the electron-donating *N*,*N*-dimethylacrylamide giving a significantly lower cross-metathesis yield than that of the electron-deficient *N*,*N*-diphenylacrylamide.[74]

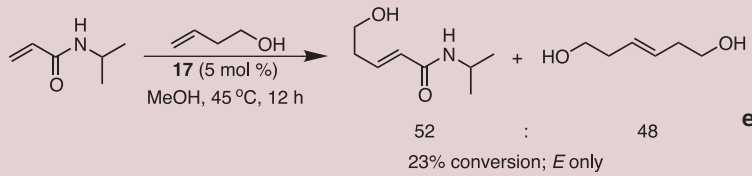
Recyclable catalyst **17** has been used in a related cross-metathesis transformation involving an α,β-unsaturated amide and a terminal olefin (**eq 17**).[76] The solid-phase catalyst **22** has also been used to facilitate the cross metathesis of *N*,*N*-dialkylacrylamides as examples of electron-deficient alkenes.[39]

Despite the obvious potential for cross metathesis in biological systems, little progress has been made in developing methods applicable to protic solvents such as methanol and water. To date, attempts to carry out selective cross-metathesis reactions in these environments have proven to be problematic. For example, cross metathesis between *N*-isopropylacrylamide and 3-butenol in methanol gave a mixture of cross-coupled and homodimer products in almost equal amounts (**eq 18**).[37] Connon and Blechert postulated that the particularly electrophilic alkylidene intermediates in these reactions are of insufficient stability in nucleophilic solvents, thus giving unselective reactions and poor yields of cross-metathesis products.[37]



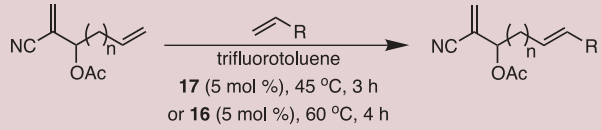

eq 17

Ref. 76




eq 18

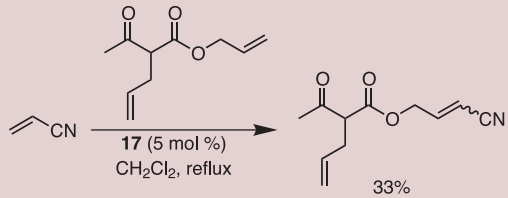
Ref. 37




| n | R | CM Yield with **16** | CM Yield with **17** | *E*/*Z* |
|---|---|---|---|---|
| 2 | $CF_3$ | 16% | 50% | ≥ 20:1 |
| 8 | $CF_3$ | > 95% | ≥ 95% | ≥ 20:1 |
| 2 | $C_4F_9$ | 13% | 57% | ≥ 20:1 |
| 8 | $C_4F_9$ | 24% | ≥ 95% | ≥ 20:1 |

eq 19

Ref. 77




eq 20

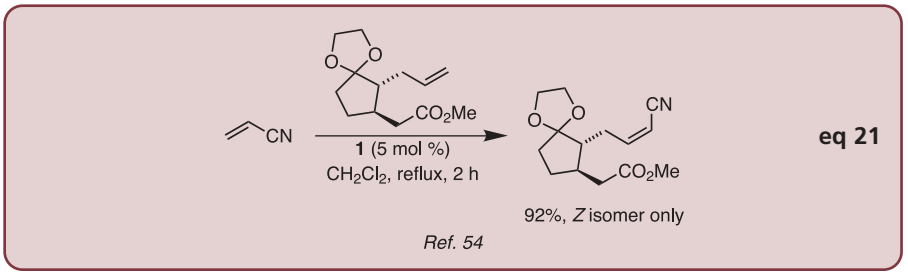
Ref. 76

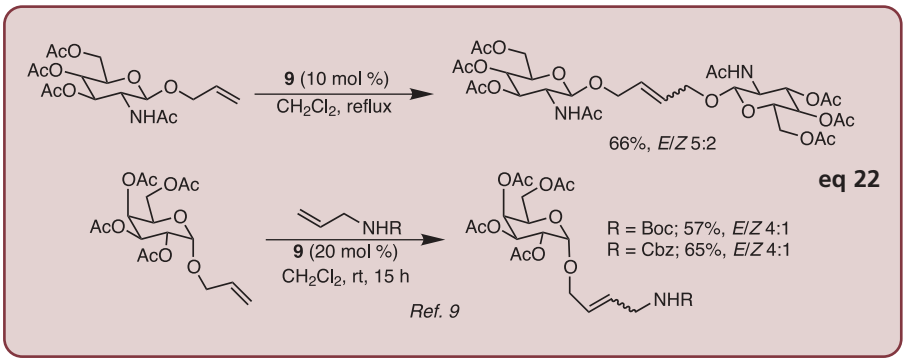
## 5.4. Acrylonitriles

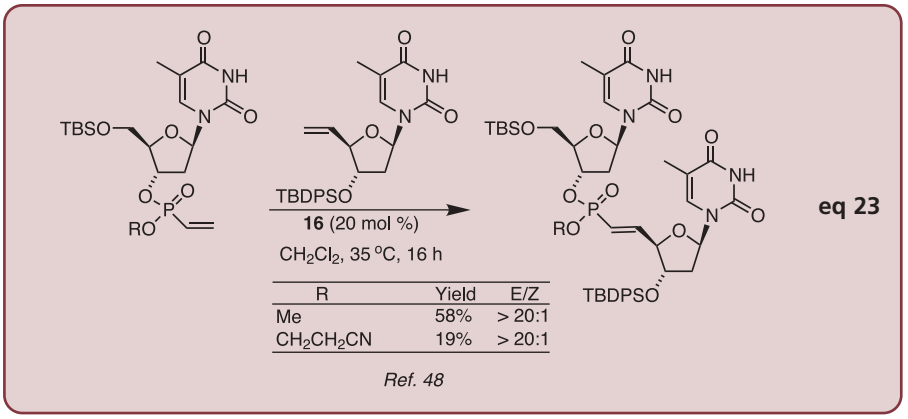
Organonitriles are useful synthetic intermediates that can be reduced to an amine or aldehyde, or hydrolyzed to the corresponding acid. These derivatives can, in theory, be prepared by cross metathesis of a suitable acrylonitrile. However, acrylonitriles tend to be unreactive in cross metathesis and, in some cases, cross metathesis of an olefin can even take place in the presence of a hindered acrylonitrile (**eq 19**).[77] Cross metathesis only occurs with the relatively electron-rich terminal double bond and not the hindered, electron-deficient nitrile double bond, when using these particular catalysts. However, the acrylonitrile functionality does participate in a competitive intramolecular RCM reaction to give a 5-membered ring. In addition, Grubbs first-generation catalyst **9** does not generally tolerate this functionality, and molybdenum catalysts are particularly sensitive and their use is often impractical. However, the emergence of second-generation, recyclable catalysts has made these reactions possible.

Hoveyda and co-workers carried out studies on acrylonitriles using catalyst **17**, with a resulting intriguing product selectivity:[38a] a homodimer was isolated in an *E*/*Z* ratio of 4:1 and the cross-metathesis product exclusively as the *Z* isomer. The authors postulate that the *Z* selectivity is the result of kinetic control, probably related to either the small size or the electron-withdrawing properties of the cyano substituent. By comparison, cross metathesis of acrylonitrile using **9** gave a product with high *E* stereoselectivity.[38b] (This is thought to be the only example reported, where first-generation Grubbs catalyst **9** promotes cross metathesis of an acrylonitrile.) Blechert and co-workers have also used catalyst **17** to facilitate cross metathesis of acrylonitriles (**eq 20**);[76] Grubbs second-generation catalyst **16** proved to be unsuitable, as it does not facilitate cross metathesis with electron-deficient alkenes.

The molybdenum complex **1** has been used in cross-metathesis reactions of acrylonitrile with a series of alkenes to give predominantly the substituted *Z* acrylonitrile products in 18–90% yields.[78] The poor nucleophilicity of an acrylonitrile dictates that its participation in cross-metathesis reactions requires a reaction partner that is more nucleophilic. This is why reactions involving styrene do not take place: both substrates (styrene and acrylonitrile) are good alkylidene donors but poor nucleophiles. In contrast to other studies,[74] yields were lower for alkyl-substituted olefins bearing a polar group in the alkyl substituent. Catalyst **1** has also been employed to prepare a chain-extended, α,β-unsaturated nitrile with high *Z* stereoselectivity (**eq 21**).[54] Crowe and co-workers have also reported the cross metathesis of unsaturated aliphatic nitriles of variable tether length between the C=C and CN groups with allylsilanes using catalyst **1**.[79] Here, the coordinating solvent dimethoxyethane was used, since it is known to stabilize reactive methylene complexes formed as intermediates in the Mo-catalyzed olefin metathesis reactions.[13]




## 5.5. Carbohydrates

The application of cross-metathesis chemistry to carbohydrate-based systems has generated considerable interest (see section 5.1.1 for a discussion of amino acid and peptide-based examples). Oligosaccharides are critical components of synthetic vaccines, drug-delivery systems and the like, and the ability to tether small, organic molecules onto these backbone structures is critical to the development of applications in these and related areas. Cross metathesis is now an important tool in this field. For example, cross metathesis has been used to provide a route to 1,4-butanediol-linked head-to-head dimers derived from daunosamine, the amino sugar group present in daunomycin, the RNA groove-binding antibiotic natural product.[80] Reaction to form the dimeric product proceeded in good yield; however, cross metathesis was sluggish for substrates containing an unprotected hydroxyl group. Roy and Das have also utilized cross metathesis in the carbohydrate arena by forming homodimers of sugar substrates and by coupling N-protected terminal allylamines with *O*-allyl glycosides (**eq 22**).[9]

## 5.6. Other Functionalities

Cross metathesis is a particularly versatile reaction that seems to tolerate a number of functional groups within the olefinic substrates. Lera and Hayes investigated the formation of vinylphosphonate-linked nucleotide dimers via a cross-metathesis reaction employing **16** as catalyst (**eq 23**).[48] The reaction proceeded in moderate yield to afford the *E* isomer as a 1:1 mixture of diastereoisomers at phosphorus. In contrast, no reaction occurred when first-generation Grubbs catalyst **9** was used. Some interesting side products, in which the benzylidene group from catalyst **16** had been transferred to the starting material, were also isolated. The cross-metathesis product had previously been prepared using palladium(0)-catalyzed P–C=C cross-coupling methodology; however, the cross-metathesis-based synthesis is significantly more effective.

Dinucleosides have been synthesized by linking an olefinic chain at the 3' position of the glycosidic moiety using cross-metathesis chemistry.[81] Yields of these dinucleotide analogs were independent of the amount of catalyst used; however, coupling was sluggish when the amine group of the heterocyclic base was unprotected. The *E* isomer was marginally favored over the *Z*, and the thymine analogue gave a noticeably lower yield than the other nucleotides.

Disubstituted olefins have been successfully employed in cross-metathesis reactions.[5,82] For example, Boc-protected *cis*-1,4-diamino-2-butene underwent cross metathesis with 9-decen-1-yl benzoate in good yield; however, an attempt to introduce a Weinreb amide gave a poor yield attributed by the authors to the coordination of the amide to catalyst **9**, consistent with observations made by Crowe and Goldberg.[78] Problems arising from the use of a Weinreb amide in cross-metathesis reactions have been overcome with the development and use of second-generation Grubbs catalyst **16**.[74]

There are other examples of cross metathesis of nitrogen-containing systems, including the reaction of allyl cyanide with allylstannanes.[64] Cross metathesis has also been used to prepare *N*,*N*'-alkenyl-substituted bis(hydrazino carbenes), a class of Fischer-type carbenes.[83] To date, there have been limited applications of cross-metathesis chemistry to this type of compound, but again the versatility and tolerance of the metathesis reaction is apparent.

Grela and Bieniek have shown that phenyl vinyl sulfone can participate in cross-metathesis reactions using second-generation catalyst **16** (**eq 24**).[24] Despite the low yield, presumably due to steric crowding in the indole starting material, this remains an efficient way to access functionalized α,β-unsaturated sulfones with excellent stereoselectivity under mild conditions.

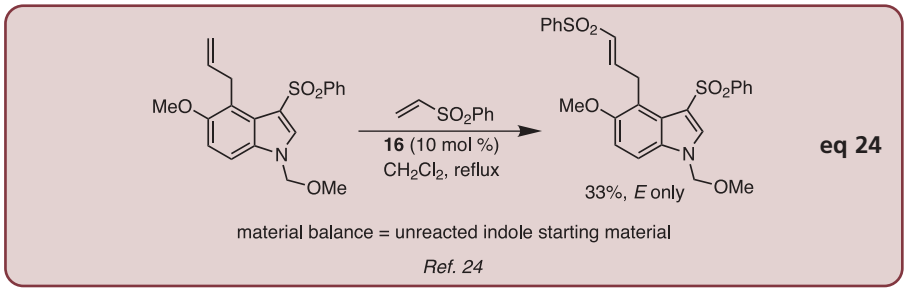
A small family of chiral 2-(2'-oxazolyl)phenols, which offer potential as novel tridentate ligands, has been synthesized using cross metathesis by Grubbs and co-workers (**eq 25**).[6] A related oxazoline underwent cross metathesis using Grubbs second-generation catalyst **16** to give the corresponding salen-like dimer in 32% yield.[6]

## 6. Ring-Opening Cross Metathesis

Ring-opening cross metathesis (ROCM or ROM-CRM) is an important strategy for assembling complex structures from readily available bicyclic substrates, since the chiral information inherent in the ring system is transformed into the stereochemistry of the cyclic product.[49b] However, metathesis reactions of this type remain relatively unexplored due to problems with lack of regioselectivity. In addition, ring-opening cross-metathesis reactions must be carried out in relatively dilute solutions to suppress competing ring-opening polymerizations. An example of the basic strategy can be seen, where a strained 2-azanorbornene derivative gives rise to a γ-lactam product in good yield in the presence of Grubbs first-generation catalyst **9** (**eq 26**).[49b] Resin-bound norbornene derivatives have also been shown to undergo metathesis with styrene to give 50/50 mixtures of regioisomers.[49b]

In another example, 4-vinylanisole reacts with a symmetrical bicyclic substrate to afford diastereomeric, cis-substituted, cyclic hydrazines in near quantitative yield (**eq 27**).[84] An analogous addition of an unsymmetrical cycloadduct to 4-vinylanisole gave four cyclic hydroxylamine products in nearly equal amounts.[84] Hydroxylamines of this type are important intermediates to conformationally restricted peptidomimetics.

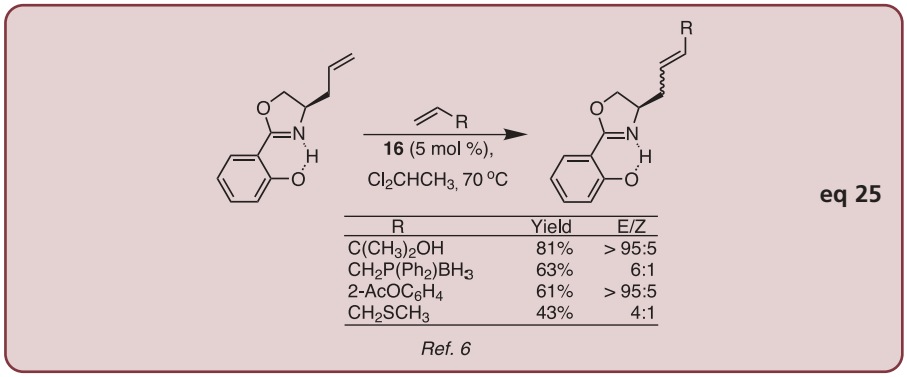
Ishikura and co-workers have reported a ring-opening cross metathesis of a 2-azabicyclo[2.2.1]hept-5-en-3-one that gives rise to two regioisomeric products, which were purified by HPLC.[85] This example reinforces the earlier point that cross-metathesis reactions tolerate a number of nitrogen-protecting groups within the substrate, e.g., Boc, Cbz, and Ac. Some work has also been done to develop the ring-opening cross-metathesis reactions of bicyclic alkenes with terminal aryl alkenes on the solid phase in an attempt to suppress competing cross-metathesis polymerizations.[86] Ring-opening polymerizations compete with the desired cross metathesis, and although this can be somewhat controlled in solution phase by using very dilute concentrations, solid-phase synthesis offers a means of preventing polymerization by isolating the bicyclic or fused alkene on a resin. The solution-phase chemistry proceeded in moderate-to-excellent yields to give two regioisomers.[86] A Wang resin bound bicyclic substrate was also reacted with an electronically diverse range of aryl alkenes, including 4-vinylanisole, to give 60–77% yields of two regioisomeric metathesis products (**eq 28**).[86]




material balance = unreacted indole starting material

*Ref. 24*

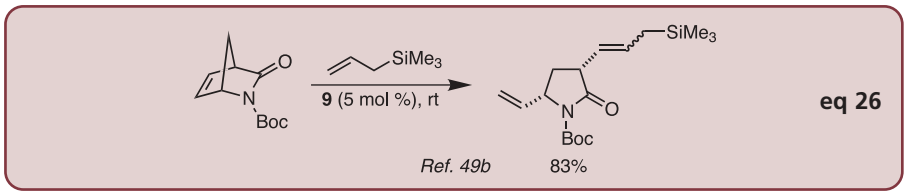
**eq 24**




| R | Yield | E/Z |
|---|---|---|
| $C(CH_3)_2OH$ | 81% | > 95:5 |
| $CH_2P(Ph_2)BH_3$ | 63% | 6:1 |
| $2\text{-}AcOC_6H_4$ | 61% | > 95:5 |
| $CH_2SCH_3$ | 43% | 4:1 |

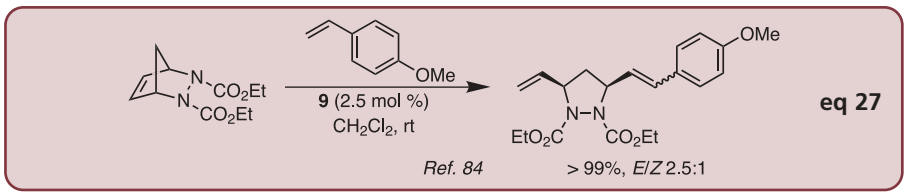
*Ref. 6*

**eq 25**



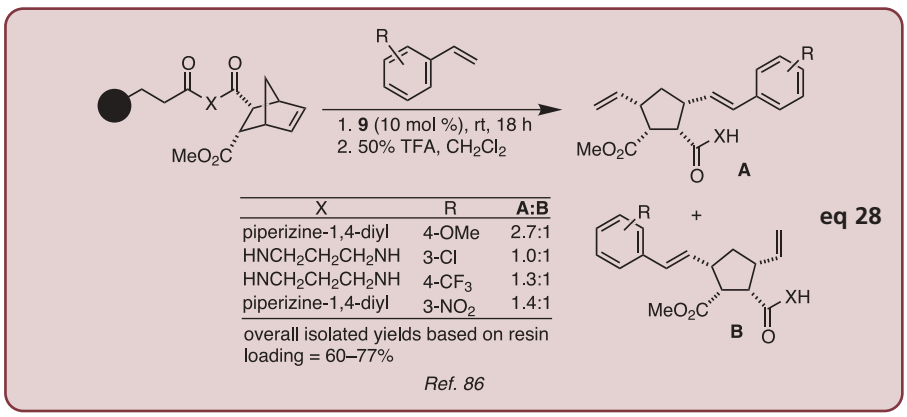

*Ref. 49b* 83%

**eq 26**




*Ref. 84* > 99%, *E*/*Z* 2.5:1

**eq 27**




| X | R | A:B |
|---|---|---|
| piperizine-1,4-diyl | 4-OMe | 2.7:1 |
| $HNCH_2CH_2CH_2NH$ | 3-Cl | 1.0:1 |
| $HNCH_2CH_2CH_2NH$ | $4\text{-}CF_3$ | 1.3:1 |
| piperizine-1,4-diyl | $3\text{-}NO_2$ | 1.4:1 |

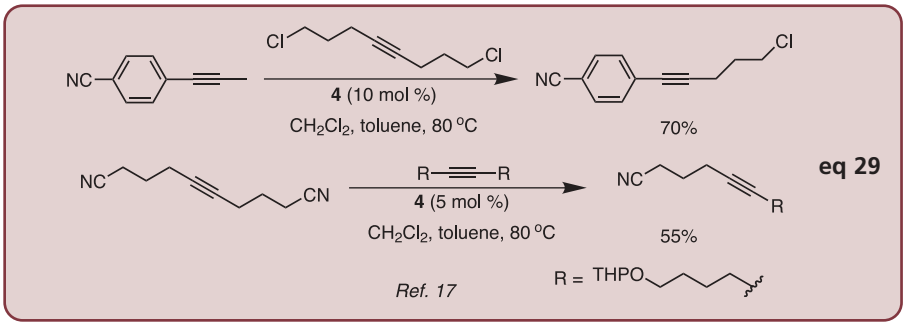
overall isolated yields based on resin loading = 60–77%

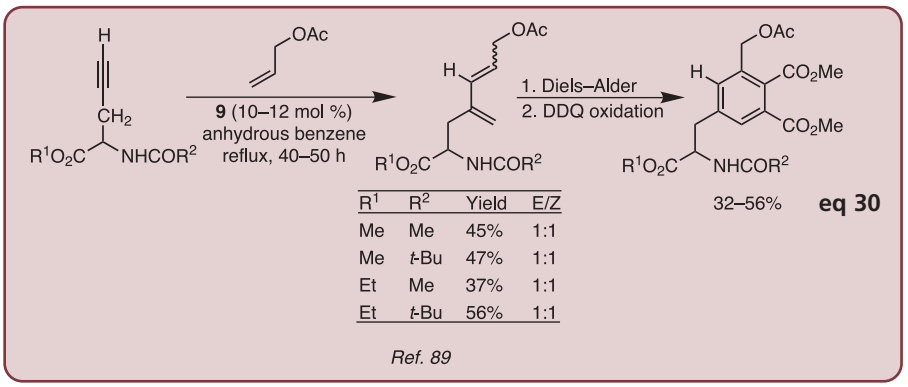
*Ref. 86*

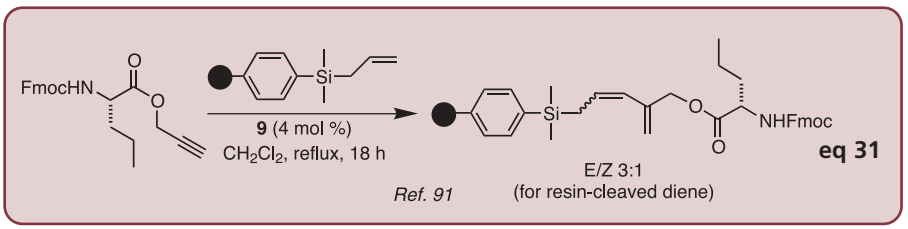
**eq 28**

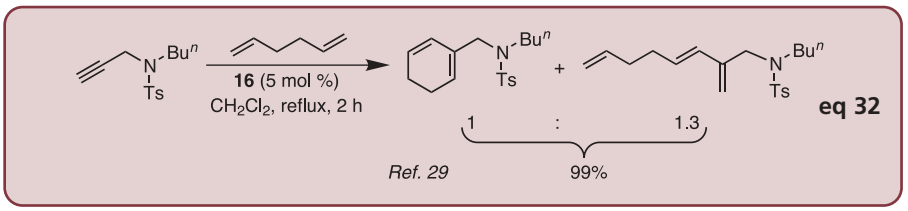
## 7. Cross Metathesis with Alkynes

Alkyne-based cross metathesis is a comparatively unexplored area of metathesis chemistry with few nitrogen-containing systems having been reported (**eq 29**).[17] One important general application of alkyne-based cross metathesis is the reaction of an alkyne and an alkene to generate a disubstituted butadiene for use in Diels–Alder chemistry. This combination of cross metathesis and Diels–Alder chemistry provides straightforward and versatile access to some structurally quite complex systems.[87,88] For example, α-amino acid




based dienes, prepared by enyne cross metathesis, undergo the Diels–Alder reaction to give functionalized phenylalanine derivatives (**eq 30**).[89] Despite the moderate yields, this method is synthetically viable, since the acetylene building blocks used are readily obtainable from glycine-derived starting materials. The lack of *E*/*Z* stereoselectivity observed in these reactions, although not desirable, is of no consequence to the final target molecule. Highly substituted tetrahydropyridines, important structural components of numerous alkaloids, have also been prepared by enyne cross metathesis followed by an aza-Diels–Alder synthetic step.[90]

Other examples include a selective, enyne cross metathesis of solid-phase-supported allylsilylpolystyrene (1% DVB) with Fmoc-protected norvaline propargyl ester—itself formed from the free carboxylic acid, Fmoc-Nva-OH (**eq 31**).[91] Reactions of this type, in which an alkyne is coupled to an alkene through cross metathesis avoid problems of homodimer formation. Blechert's group demonstrated other applications in this area with the synthesis of pseudooligosaccharides.[92] There is significant scope in this methodology, since a range of sugars and dienophiles can be employed.[92]

Tandem enyne cross metathesis between an alkyne and 1,5-hexadiene, followed by in situ ring-closing metathesis, has also been carried out using second-generation catalyst **16** (**eq 32**).[29] The crude diene products were subsequently subjected to a Diels–Alder reaction with *N*-methylmaleimide to give bicyclic products of substantially greater molecular complexity than the alkene and alkyne starting materials.

## 8. Conclusions

While cross-metathesis chemistry is yet to reach the maturity level of other metathesis-based methodologies, it has already made a significant impact in the area of nitrogen-containing systems. The mild conditions under which these reactions can be performed, along with the high functional-group tolerance of the current catalysts, mean that cross metathesis will clearly be of significant value in many areas of chemistry. There are numerous other cross-metathesis-based methodologies, including domino metathesis, which is a combination of ring-opening (ROM), ring-closing (RCM), and cross (CM) metatheses. Although domino metathesis is a useful method for the synthesis of various novel cyclic compounds, it is not discussed in this review. Original articles and reviews of this topic, including discussions of stereospecificity and regiocontrol, have recently been published.[10,93]

## 9. Acknowledgments

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## 10. References and Notes

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## About the Authors

Andrea Vernall was born in 1981 in Wellington, New Zealand. In 2002, she obtained a Bachelor of Science with First Class Honours in Chemistry from the University of Canterbury. Currently a member of Professor Abell's research group, she is in her second year of a Ph.D. research program investigating metathesis reactions in biological systems.

Andrew Abell was born in 1960 in Adelaide, South Australia. He obtained a Bachelor of Science with First Class Honours in Organic Chemistry from the University of Adelaide in 1982 and, in 1986, he received his Ph.D. from the same university under the supervision of Dr. Ralph Massy-Westropp. Two years were then spent working as a postdoctoral fellow with Professor Sir Alan Battersby at Cambridge, UK and, in 1987, he took a faculty position at the University of Canterbury, Christchurch, New Zealand. His current research interests include the design, synthesis, and biological properties of peptidomimetics.

# Ruthenium-Based Metathesis Catalysts

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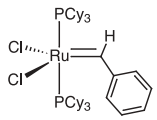
### Grubbs Catalyst 1st Generation

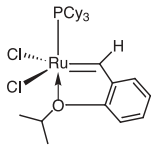
**57,972-6** — 1g, 5g




The first metathesis catalyst to be widely utilized in organic synthesis, Grubbs First Generation Catalyst effects ring-closing metathesis, olefin cross-metathesis, and ROMP with high activities and tolerance for functional groups and protic media.[1,2]

### Hoveyda–Grubbs Catalyst 1st Generation

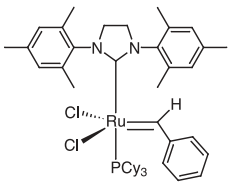
**57,794-4** — 100mg, 500mg, 2g




An efficient, recyclable catalyst for RCM of terminal olefins.[6,7]

### Grubbs Catalyst 2nd Generation

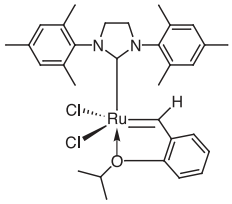
**56,974-7** — 100mg, 500mg, 2g




Grubbs Second Generation Catalyst is a more active analog of the first-generation Grubbs catalyst for ring-closing metathesis, cross metathesis, and ROMP,[3] and can lead to trisubstituted olefins via cross metathesis;[4] it ring-closes olefins with excellent functional-group tolerance and selectivity.[5]

### Hoveyda–Grubbs Catalyst 2nd Generation

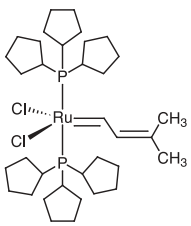
**56,975-5** — 100mg, 500mg, 2g




The Hoveyda–Grubbs Second Generation catalyst shows efficiencies similar to those of second-generation Grubbs catalyst, but with different substrate specificities. The catalyst is unique in catalyzing the ring-closing, ring-opening, and cross-metathesis reactions of highly electron-deficient substrates.[7,8]

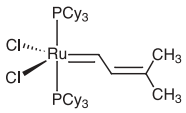
### Dichloro(3-methyl-2-butenylidene)bis(tricyclopentylphosphine)ruthenium(II)

**57,870-3** — 1g, 5g




### Dichloro(3-methyl-2-butenylidene)bis(tricyclohexylphosphine)ruthenium(II)

**57,868-1** — 1g, 5g




**References:** (1) Schwab, P. et al. *J. Am. Chem. Soc.* **1996**, *118*, 100. (2) Miller, S. J. et al. *ibid.* **1996**, *118*, 9606. (3) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (4) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751. (5) (a) Scholl, M. et al. *ibid*. **1999**, *1*, 953. (b) Saito, N. et al. *ibid*. **2002**, *4*, 803. (6) Kingsbury, J. S. et al. *J. Am. Chem. Soc.* **1999**, *121*, 791. (7) Garber, S. B. et al. *ibid.* **2000**, *122*, 8168. (8) Randl, S. et al. *Synlett* **2001**, 430.

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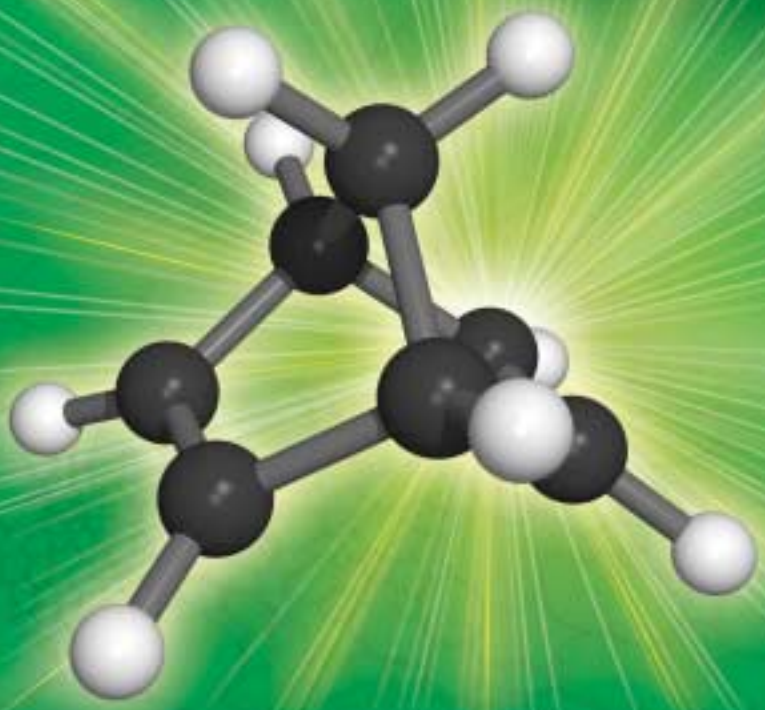

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| 8.0 | 10 | 10/30 | Z51,216-8 | Z51,217-6 | Z51,264-8 |
| 9.5 | 11.5 | | Z51,249-4 | Z51,256-7 | Z51,265-6 |
| 11.0 | 13 | | Z51,250-8 | Z51,257-5 | Z51,266-4 |
| 12.5 | 14.5 | 14/20 | Z51,211-7 | Z51,212-5 | Z51,267-2 |
| 14.0 | 16.5 | | Z51,251-6 | Z51,258-3 | Z51,268-0 |
| 16.0 | 18 | Sure/Seal™ | Z51,218-4 | Z51,219-2 | Z51,269-9 |
| 17.5 | 19.5 | 19/22 | Z51,220-6 | Z51,221-4 | Z51,270-2 |
| 19.0 | 21 | | Z51,252-4 | Z51,259-1 | Z51,271-0 |
| 20.5 | 23 | 24/40 | Z51,213-3 | Z51,214-1 | Z51,272-9 |
| 22.0 | 25 | | Z51,253-2 | Z51,260-5 | Z51,273-7 |
| 24.0 | 26.5 | | Z51,254-0 | Z51,261-3 | Z51,274-5 |
| 25.5 | 28 | 29/42 | Z51,222-2 | Z51,223-0 | Z51,275-3 |
| **Mixed set of 130 septa with case** | | | Z51,276-1 | Z51,278-8 | Z51,279-6 |

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| 2/60 | 38–400 | Z54,754-9 |
| 4/125 | 48–400 | Z54,755-7 |
| 8/250 | 58–400 | Z55,096-5 |
| 16/500 | 70–400 | Z55,097-3 |

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| 2/60 | 38–400 | Z55,100-7 |
| 4/125 | 48–400 | Z55,102-3 |
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| 2/60 | 38–400 | Z55,122-8 |
| 4/125 | 48–400 | Z55,123-6 |
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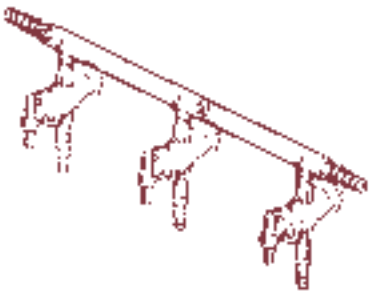
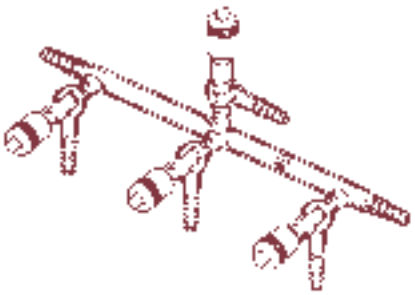


### Glass Stopcock

| Positions | Overall L (mm) | Cat. No. |
|---|---|---|
| Standard manifold | | |
| 3 | 300 | Z53,213-4 |
| 4 | 400 | Z53,214-2 |
| 5 | 500 | Z53,215-0 |
| Manifold with vacuum-gauge port | | |
| 3 | 300 | Z53,216-9 |
| 4 | 400 | Z53,217-7 |
| 5 | 500 | Z53,218-5 |



### High-Vacuum PTFE Valve

| Positions | Overall L (mm) | Cat. No. |
|---|---|---|
| Standard manifold | | |
| 3 | 300 | Z53,219-3 |
| 4 | 400 | Z53,220-7 |
| 5 | 500 | Z53,221-5 |
| Manifold with vacuum-gauge port | | |
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| 4 | 400 | Z53,223-1 |
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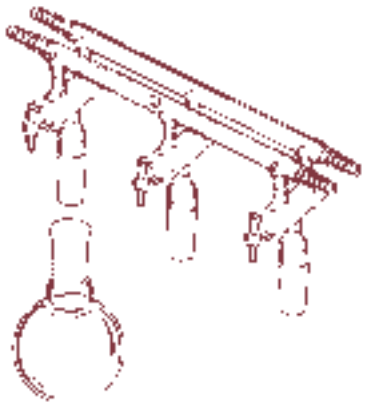

| Positions | Overall L (mm) | Ʇ*14/20* Cat. No. | Ʇ*24/40* Cat. No. | Ʇ*29/32* Cat. No. |
|---|---|---|---|---|
| 3 | 300 | Z53,066-2 | Z53,069-7 | Z51,752-6 |
| 4 | 400 | Z53,067-0 | Z53,070-0 | Z51,753-4 |
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|---|---|---|
| 3 | 225 | Z53,072-7 |
| 5 | 305 | Z53,073-5 |
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# Solutions for Oligonucleotide Synthesis

**Precisely Blended** Capping, Deblocking, and Activator solutions for oligonucleotide synthesis.

| Catalog No. | Product Name | Unit |
|---|---|---|
| 55,534-7 | **Cap Mix A**<br>(Contains 90% tetrahydrofuran: 10% acetic anhydride) | 1L<br>2L |
| 55,531-2 | **Cap Mix A, with 2,6-lutidine**<br>(Contains 80% tetrahydrofuran: 10% acetic anhydride: 10% 2,6-lutidine) | 1L<br>2L |
| 55,533-9 | **Cap Mix A, with pyridine**<br>(Contains 80% tetrahydrofuran: 10% acetic anhydride: 10% pyridine) | 1L<br>2L |
| 55,532-0 | **Cap Mix B**<br>(Contains 84% tetrahydrofuran: 16% 1-methylimidazole) | 1L<br>2L |

| Catalog No. | Product Name | Unit |
|---|---|---|
| 55,535-5 | **Cap Mix B, with pyridine**<br>(Contains 80% tetrahydrofuran: 10% pyridine: 10% 1-methylimidazole) | 1L<br>2L |
| 56,193-2 | **Deblock**<br>(Contains 3% trichloroacetic acid in dichloromethane) | 1L<br>2L |
| 55,404-9 | **Activator**<br>(1*H*-Tetrazole, 3 wt. % solution in acetonitrile) | 1L<br>2L |

**For additional pre-blended solvents or larger container options, email us at labchem@sial.com.**

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