

# Addition of Organochromium Reagents to Carbonyl Compounds

Kazuhiko Takai, Okayama University, Tsushima, Okayama, Japan

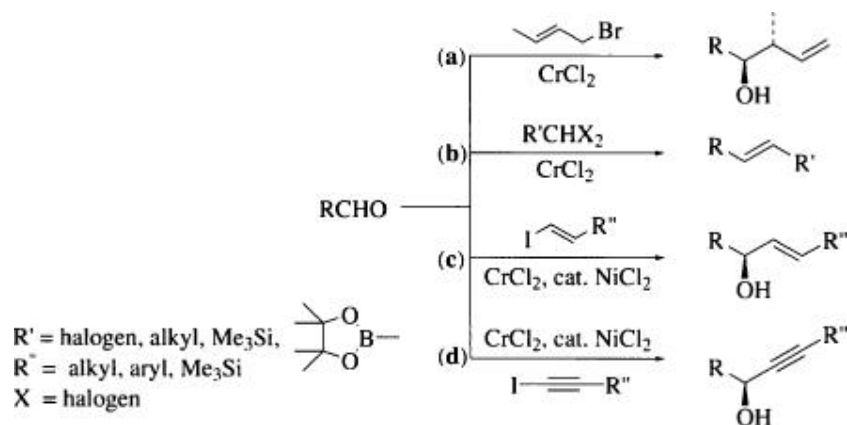
## 1. Introduction

Organochromium compounds can be prepared by two methods: (1) transmetallation from the corresponding organolithium, — magnesium, or — zinc compounds with chromium(III) halides, and (2) reduction of organic substrates, such as organic halides and unsaturated compounds, with chromium(II) salts. However, because the first method suffers from low solubility of chromium(III) salts in ethereal solvents and difficulty in preparing organolithium compounds, especially those with highly oxygenated substituents, preparation of organochromium reagents is usually performed by the second method.

Low-valent chromium species are reducing agents. The reduction of organic substrates with the chromium(II) species under aqueous conditions was extensively studied by Castro, Kochi, and Hanson. (1-4) In order to employ this reduction for carbon-carbon bond formation, aprotic conditions are preferred. Reduction of various types of organic halides and compounds having unsaturated or hetero-hetero bonds with the chromium(II) species is discussed in the [Mechanism](#) Section. Also described are the transmetallation to organochromium compounds from other organometallics, the nature of carbon-chromium bonds, and the X-ray structure of organochromium compounds.

Reactions of organochromium reagents with carbonyl compounds are described in the Scope and Limitations section which is divided into several subsections according to the organic groups on the organochromium reagents. The first part covers allylic chromium reagents ([Scheme 1](#), path a). In 1977, Hiyama and Nozaki developed a preparation of chromium(II) species from chromium(III) chloride with lithium aluminum hydride in an *aprotic* solvent. (5) They reported the addition of allylic chromium reagents, derived by reduction of allylic halides with the chromium(II) species, to carbonyl compounds in a chemoselective manner. In the next year, Heathcock reported that the coupling products between the crotylchromium reagent and aldehydes have mainly the anti configuration. (6) The commercial availability of anhydrous chromium(II) chloride led to the widespread application of the reagents for 1,2-diastereoselective construction of carbon skeletons.

**Scheme 1.**



In the second part of the Scope and Limitations section, geminal dichromium reagents developed by Takai are described. One of the weak points of the Wittig reaction is the transformation of aldehydes into alkenyl halides having the E configuration. This was overcome with the introduction of geminal dichromium reagents derived by reduction of geminal dihalides with chromium(II) salts (Scheme 1, path b). (7, 8) Reduction of alkenyl and aryl halides with chromium(II) chloride leading to the corresponding organochromium reagents and their addition to aldehydes was discovered in 1983 by Hiyama, Takai, and Nozaki (Scheme 1, path c). (9) However, it was proved by Takai that the commercial chromium(II) chloride employed contained a catalytic amount of a nickel salt and that the salt was indispensable to promote the coupling reaction. (10) At the same time, Kishi independently discovered this catalytic effect of nickel, and applied the protocol to the total synthesis of palytoxin. (11) A catalytic amount of nickel also accelerates the preparation of alkynylchromium reagents from alkynyl halides with chromium(II) chloride (Scheme 1, path d), (12) and the reagents are employed especially to construct compounds with a conjugated endiyne moiety. (13, 14) These chromium-nickel reagents are discussed in the third part of the section. Alkylchromium and other organochromium reagents are described in the last parts of the section.

In 1996, Fürstner developed a method using catalytic amounts of a chromium salt in combination with stoichiometric quantities of manganese metal as reductant. (15) Subsequently, asymmetric reactions with chiral chromium complexes using this method were reported. (16) To date, several reviews have dealt with organochromium reagents. (17-25)

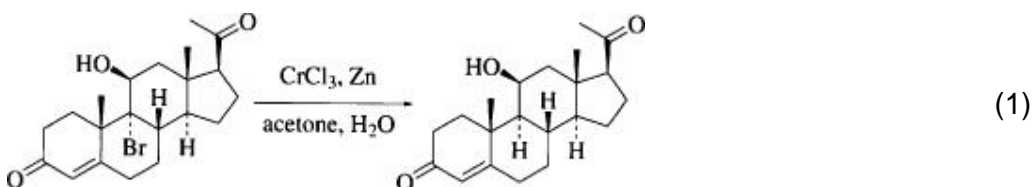
The literature has been surveyed up to October 2001.

## 2. Preparation, Properties, and Mechanisms of Reactions of Organochromium Reagents

### 2.1. Low-Valent Chromium as a Reducing Agent

#### 2.1.1.1. Protic Conditions

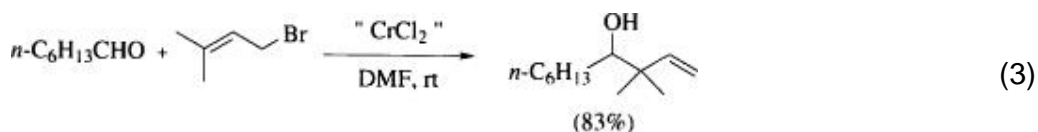
The chromium(II) ion has been employed as a reducing agent for more than 60 years and can be prepared either by reduction of chromium(III) salts or by dissolving chromium metal in deoxygenated acid. (4) The standard reduction potential ( $E^0$ ) of chromium(III) to chromium(II) measured in water is  $-0.407$  V, which is lower than that for zinc(II) to zinc(0) ( $-0.762$  V). Therefore, zinc has been employed as a reductant for chromium(III) salts under aqueous and nonaqueous conditions. (1, 2, 26-28) This method, however, simultaneously introduces zinc ions and, in some cases, zinc metal into the system, which can lead to different results than for reactions with pure chromium(II) ion. The dissolution of chromium metal in an acid provides zinc-free chromium(II) ions, but is limited to aqueous conditions. (29-31) Chromium(II) salts, such as chromium(II) perchlorate, chromium(II) sulfate, and chromium(II) acetate, are prepared in this way. The chromium(II) ion is then used for reductions such as deoxygenation or dehalogenation. (32) Reduction of reactive halides (or pseudo halides) such as  $\alpha$ -halo ketones, allylic halides, benzylic halides, and polyhalides with chromium(II) ions proceeds smoothly. Since the chromium(II) ion is typically prepared in water, the organochromium compounds produced are usually hydrolyzed to dehalogenated compounds (Eq. 1). (30, 33, 34)



#### 2.1.1.2. Aprotic Conditions

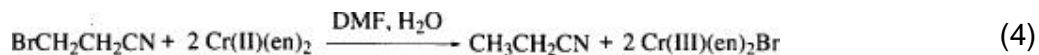
Because carbon-chromium bonds are not polar compared to carbon-magnesium bonds, the bonds are not very sensitive to a small amount of water. However, the carbon-chromium bonds are hydrolyzed in aqueous solvents, so it is necessary to generate organochromium species under aprotic conditions in order to conduct carbonyl additions with the latter species. A convenient preparation of chromium(II) species in aprotic solvents by reduction of chromium(III) chloride with a 0.5 molar equivalent of lithium aluminum hydride in tetrahydrofuran was first reported by Hiyama and Nozaki in 1977 (Eq. 2). (5) Anhydrous chromium(II) species enable organochromium

compounds to be prepared by reduction of organic halides under anhydrous conditions, and thus, greatly expands the scope of carbon-carbon bond forming reactions via organochromium reagents. Reductive coupling of allylic and benzylic halides, (35) reduction of geminal dihalocyclopropanes, (35) and the Grignard-type addition of allylic chromium compounds to carbonyl compounds (Eq. 3) (5) are achieved by using chromium(II) species.

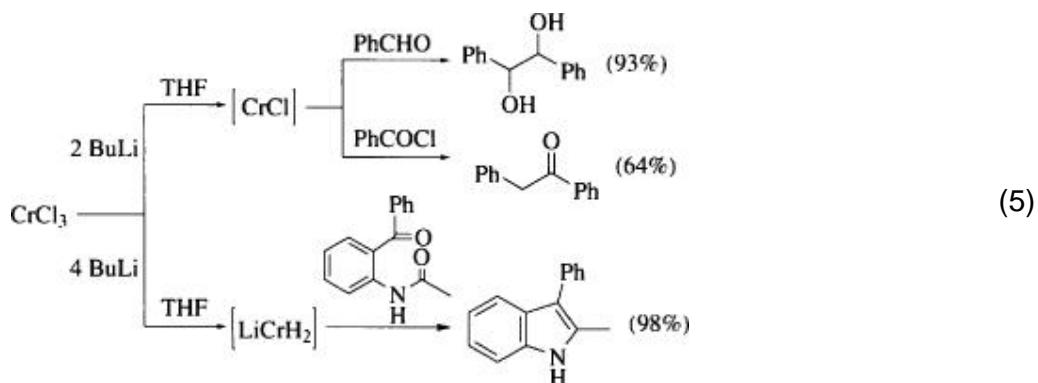


Anhydrous chromium(II) chloride produced by the reduction of chromium(III) chloride with hydrogen (36) is commercially available and can be used without further purification. Chromium(II) chloride is gray, very hygroscopic, and oxidizes rapidly in air, especially under moist conditions, to give green-colored chromium(III). Chromium(II) chloride is only slightly soluble in anhydrous tetrahydrofuran or dioxane, and reactions performed in these solutions are usually heterogeneous. The salt, however, is solubilized in tetrahydrofuran by addition of 2 equivalents of lithium chloride. Also, the salt is soluble in dimethylformamide and dimethyl sulfoxide. Chloride-free chromium(II) is prepared by reduction of chromium(III) bromide with lithium aluminum hydride. (8)

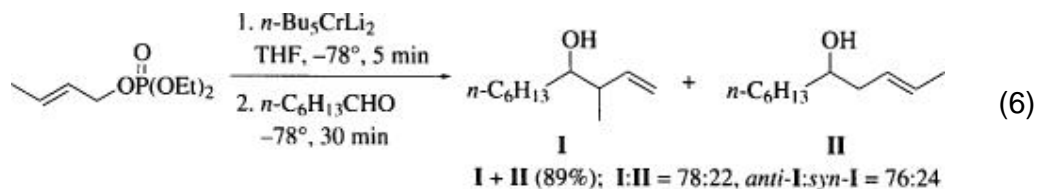
The reducing power of chromium(II) is less than that of magnesium(0) and samarium(II). Thus, aliphatic aldehydes and ketones remain unchanged when treated with chromium(II) in tetrahydrofuran or dimethylformamide. The reducing power of chromium(II) increases by complexation with electron-donating ligands such as ethylenediamine. As a consequence, alkyl halides are reduced to the corresponding alkane in aqueous media by the amine-complexed chromium(II) species (Eq. 4). (37-39) Such an enhancement of reducing power is also observed under aprotic conditions. For example, reduction of organic halides in tetrahydrofuran is accelerated by addition of one or two equivalents of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) or *N,N*-dimethylformamide.



When *n*-butyllithium is added to a suspension of chromium(III) chloride in tetrahydrofuran, many low-valent chromium species are generated, depending on the amount of *n*-butyllithium, and some of the species have been characterized. For example, addition of two equivalents of *n*-butyllithium gives CrCl via reductive elimination from chlorodibutylchromium(III). (40) Addition of four equivalents of *n*-butyllithium gives LiCrH<sub>2</sub> (Eq. 5). (41) Such reactive species, including chromium ate complexes, act as reducing agents for organic substrates.



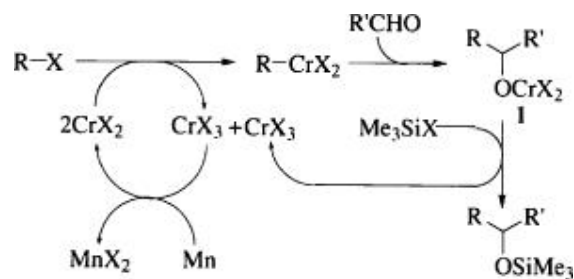
Allyl and propargyl anion species are generated by treatment of the corresponding diethylphosphates with “*n*-Bu<sub>5</sub>CrLi<sub>2</sub>” derived from chromium(III) chloride and 5 equivalents of *n*-butyllithium in tetrahydrofuran (Eq. 6). (42) The product distribution of the reaction between heptanal and crotyl phosphate suggests that the reactive species derived from the phosphate and “*n*-Bu<sub>5</sub>CrLi<sub>2</sub>” is not the same as that generated with chromium(II) chloride.



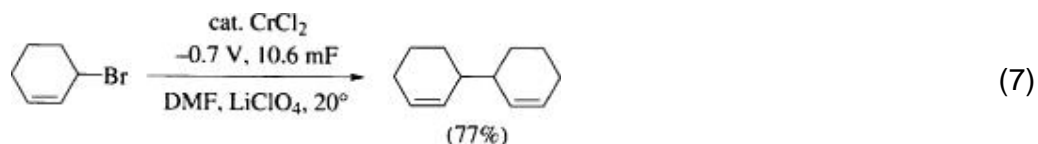
### 2.1.1.3. Recycling of Chromium(II)

Chromium(II) is a one-electron reductant; therefore 2 equivalents are required for the formation of organochromium reagents. Several approaches for recycling a catalytic amount of chromium(II) salts have been reported. One of the methods is to reduce the chromium(III) with a stronger reducing metal. (15, 43, 44) A combination of manganese and chlorotrimethylsilane is suitable for this purpose because (Scheme 2): 1) Manganese metal does not directly reduce organic halides (R-X) under the reaction conditions; 2) The chromium(III) bound to the oxygen of the initial carbonyl addition product **1** is smoothly replaced by chlorotrimethylsilane to liberate a chromium(III) salt. The method can be applied to chromium(II)- and chromium(II)-nickel(II)-mediated reactions (see below). Although the reducing power of zinc(0) is stronger than that of chromium(II), zinc can only be employed for the reduction of chromium(III) in a few cases, because zinc reduces alkyl halides directly to generate organozinc species, and thus the merits of the organochromium chemistry disappear.

**Scheme 2.**



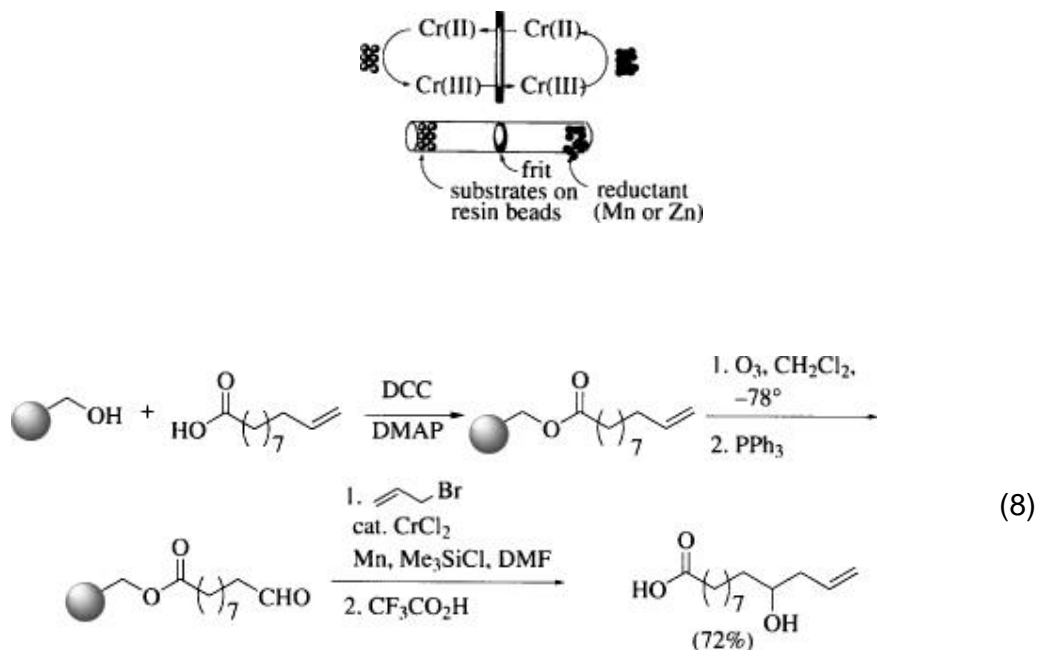
A second method for recycling chromium(II) is the electrochemical reduction of chromium(III) to chromium(II), which takes place in dimethylformamide at a glass carbon cathode with a potential of  $-0.4$  V (vs. a Cd/Hg reference electrode). Reductive coupling of allylic and benzylic halides proceeds to give dimers in the presence of a catalytic amount of chromium(II) chloride, and this is regenerated continuously by reduction at  $-0.7$  V (Eq. 7). (45-47)



Another convenient method to reduce the amount of chromium has been developed (Scheme 3). An organic aldehyde is supported on a Wang resin and is separated from the reductant manganese by a frit. Chromium(II) is

recycled by shaking in order to promote passage of chromium(III) and chromium(II) across the frit (Eq. 8). (48)

Scheme 3.

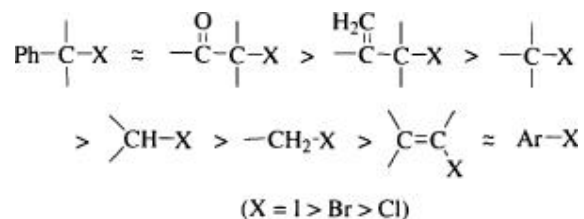


## 2.2. Reduction of Organic Halides

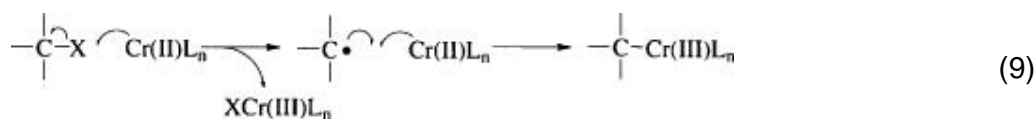
### 2.2.1.1. Alkyl Halides

Organochromium compounds can be prepared by the reduction of organic halides with chromium(II) ions. The rate of reduction of organic halides with chromium(II) salts depends on the nature of the organic group, the halide, and the reaction conditions (solvents, ligands, temperature). The reactivity of the various halides toward chromium(II) salts decreases in the order shown in Scheme 4. (1, 37)

Scheme 4.

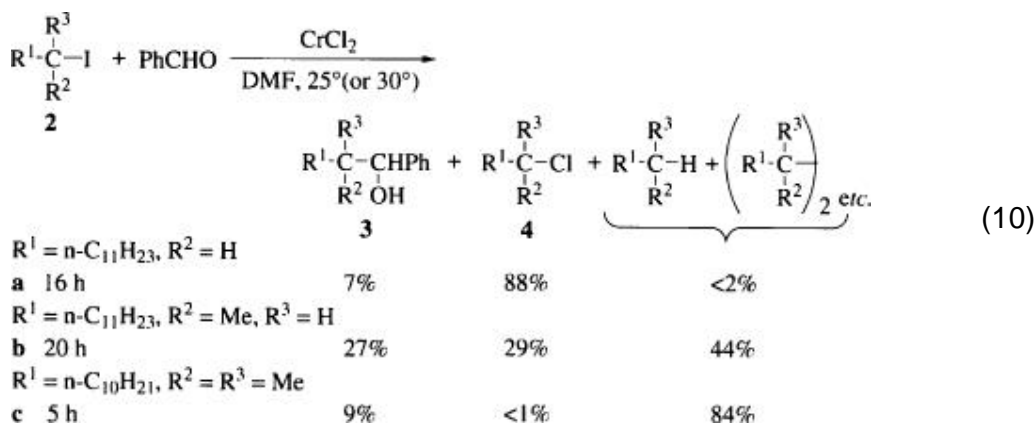


The mechanism for reduction of organic halides with chromium(II) salts has been well studied, especially for the reaction under aqueous conditions (Eq. 9). (1, 2)

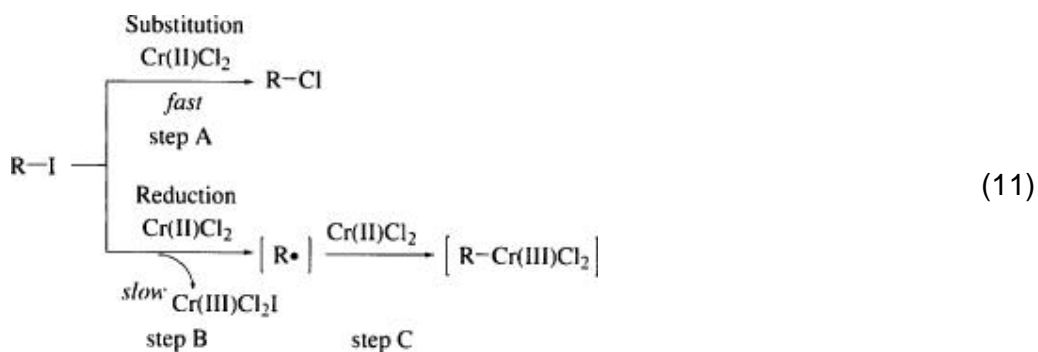


The initial and rate-determining step in the reduction is the attack of chromium(II) ion on a halogen atom, resulting in the transfer of the halogen atom from carbon to chromium. Subsequently, a free alkyl radical is produced, which reacts rapidly with a second equivalent of chromium(II) to form a new carbon-chromium bond. A one-electron transfer from the chromium(II) ion through a bridging anion was also postulated (3) because the presence of a halogen ion in the reaction mixture accelerates the second reduction step. (28, 49) Subsequent decomposition of the alkylchromium intermediate by protonolysis (in aqueous solution),  $\beta$ -hydride elimination, or attack on unreacted organic halides or other electrophiles, accounts for most of the products.

The reducing power of chromium(II) decreases in aprotic solvents, and therefore it is more difficult to reduce simple alkyl halides leading to alkylchromium(III) compounds under these conditions. The rate of reduction of alkyl iodides depends on their substitution pattern. For example, treatment of a mixture of 1-iodododecane (2a,  $R^1 = n\text{-C}_{11}\text{H}_{23}$ ,  $R^2 = R^3 = \text{H}$ ) with chromium(II) chloride in dimethylformamide at 30° for 16 hours produces only 7% of Grignard-type adduct 3a, while most of the material is recovered as 1-chlorododecane (4a, 88%, Eq. 10). (50) The rate of substitution of the primary alkyl iodide by chloride ions is higher than the reduction by chromium(II) ions under aprotic conditions (Eq. 11). (51)



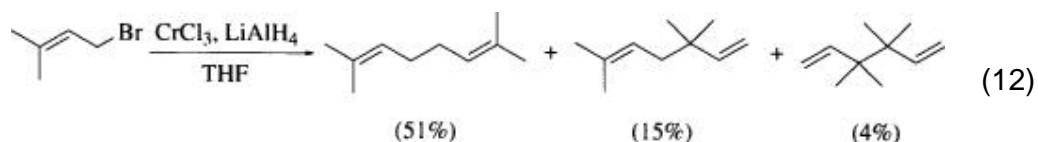




In contrast to primary alkyl iodides, reduction of secondary or tertiary alkyl iodides leading to radical or anionic species proceeds easily under the same conditions (Eq. 11). (50) Treatment of a mixture of secondary alkyl iodide **2b** ( $R^1 = n\text{-C}_{11}\text{H}_{23}$ ,  $R^2 = \text{Me}$ ,  $R^3 = \text{H}$ ) and benzaldehyde with chromium(II) chloride in dimethylformamide at  $25^\circ$  for 20 hours gives adduct **3b** in 27% yield together with alkyl chloride **4b** in 29% yield. Alkyl radical derived dimer and alkane are also produced in 44% combined yields. In the case of tertiary alkyl iodide **1c** ( $R^1 = n\text{-C}_{10}\text{H}_{21}$ ,  $R^2 = R^3 = \text{Me}$ ), Grignard-type adduct **2c** is produced in 9% yield and most of the iodide is converted into the compounds derived from the alkyl radical.

#### 2.2.1.2. Allylic and Benzylic Halides

In contrast to alkyl iodides, both steps B and C in Eq. 11 are accelerated in the case of active halides. For example, allyl and benzyl halides are smoothly reduced with chromium(II) salts in aprotic solvents to furnish allyl- and benzylchromium compounds, respectively, which then undergo homocoupling (Eq. 12). (35) When carbonyl compounds are in the reaction mixture, the allylic chromium species can be trapped to give homoallylic alcohols (see the [Scope and Limitations](#) section). (5)

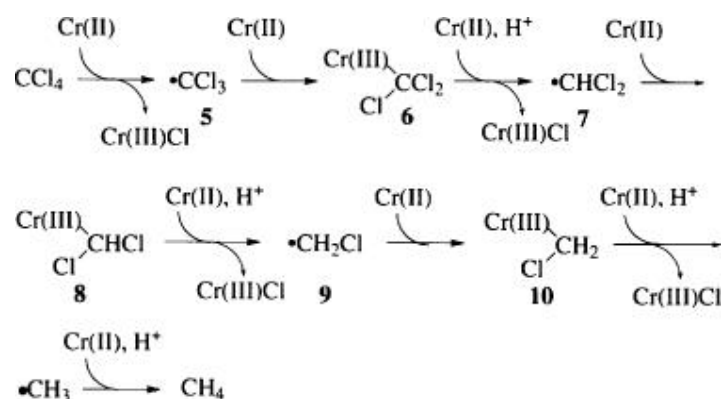


The relative rates of reduction of allyl iodide, allyl bromide, and allyl chloride to propene in protic solvents are approximately 4:4:1. (1)

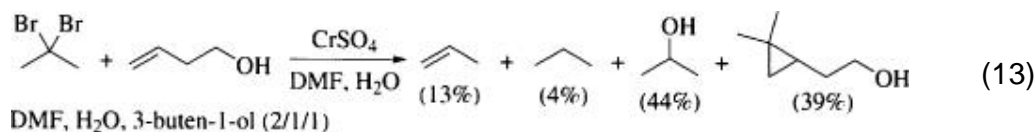
#### 2.2.1.3. Polyhalides

The reduction of geminal halides with chromium(II) sulfate in aqueous dimethylformamide proceeds rapidly at room temperature. (52) Diiodomethane, dibromomethane, chloroform and even carbon tetrachloride are reduced to methane with chromium(II) sulfate. The reduction process does not proceed via stepwise reduction ( $\text{CCl}_4 \rightarrow \text{CHCl}_3 \rightarrow \text{CH}_2\text{Cl}_2 \rightarrow \text{CH}_3\text{Cl} \rightarrow \text{CH}_4$ ), but instead involves  $\alpha$ -halomethyl radicals **5**, **7**, and **9** and the corresponding carbenoid species **6**, **8**, and **10** (Scheme 5).

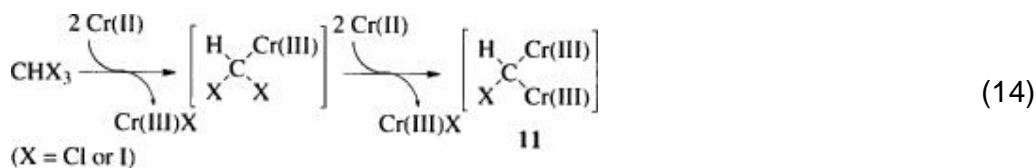
Scheme 5.



The carbenoids generated under these conditions are electrophilic; thus, Simmons-Smith-type cyclopropanation takes place in the presence of 3-buten-1-ol (Eq. 13). (52)

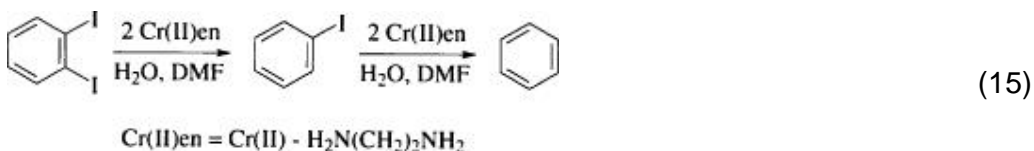


The mechanism for reduction of polyhalides in aprotic solvents is different from that in Scheme 5. First, protonation does not take place before workup, and second, further reduction leads to geminal dichromium compounds **11** (Eq. 14). (8, 7) Reactions of the geminal dichromium species **11** with aldehydes are discussed in the Scope and Limitations section. Successive reduction leading to geminal dichromium compounds is also observed with 1,1,1-trichloroalkanes (53, 54) and carbon tetrachloride. (55)



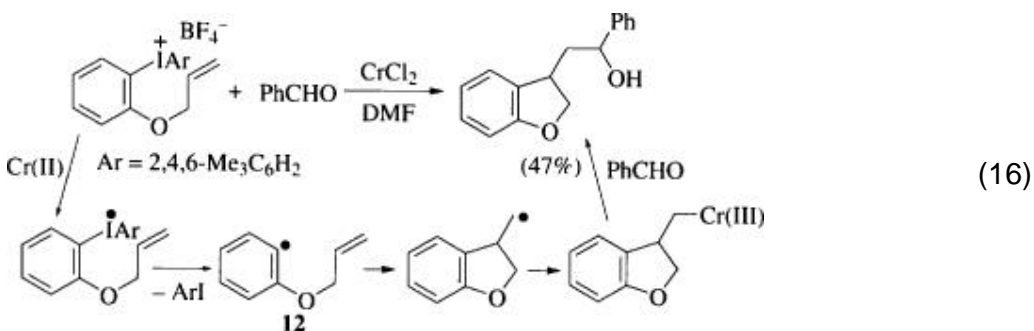
#### 2.2.1.4. Aryl and Alkenyl Halides

In protic solvents, stepwise reduction of *o*-diiodobenzene to benzene takes place with a chromium(II)-ethylenediamine complex (Eq. 15). (38) Iodobenzene is formed in high yield when less than stoichiometric amounts of the chromium(II) complex are employed.



In contrast, no reduction takes place with chromium(II) salts in aprotic solvents. Iodobenzene and 1-iodododecene are recovered unchanged when treated with chromium(II) chloride in dimethylformamide at 25°. (10) However, aryl- and alkenyl-chromium species can be prepared from the corresponding halides via transmetalation with chromium(II) chloride and a catalytic amount of nickel (see the [Scope and Limitations](#) section).

Electron-deficient diaryliodonium salts are reduced by chromium(II) to give arylchromium(III) species via aryl radicals. The intermediate aryl radical **12** can be trapped in an intramolecular manner (Eq. 16). (56, 57)



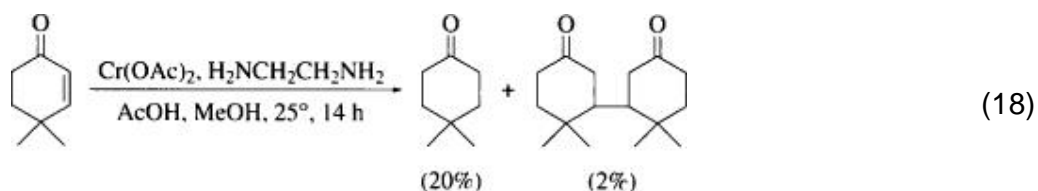
### 2.3. Reduction of Unsaturated Bonds

The reduction of carbon-carbon multiple bonds with chromium(II) under protic conditions was extensively studied by Castro and House. (58-60) The reduction proceeds easily when electron-withdrawing groups, such as carbonyl or nitrile groups, are attached to the unsaturated bonds (Eq. 17). (59) Also, the electron

transfer from chromium(II) is accelerated by addition of electron-donating ligands such as ethylenediamine.

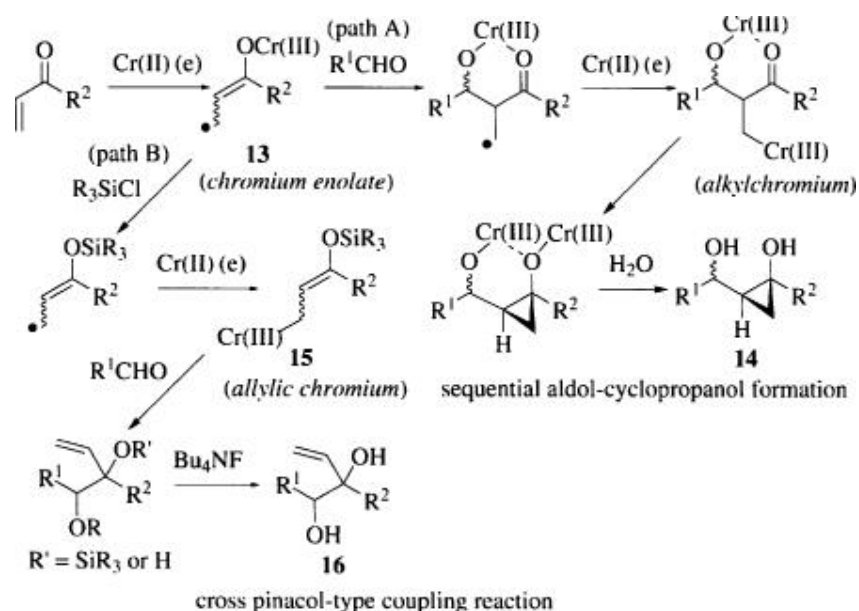


One-electron reduction of  $\alpha$ ,  $\beta$ -unsaturated ketones with chromium(II) generates a chromium enolate radical. When the reduction is conducted under protic conditions, saturated ketones are obtained by protonation. In some cases, a dimer derived by the coupling reaction of the radical is produced (Eq. 18). (60)



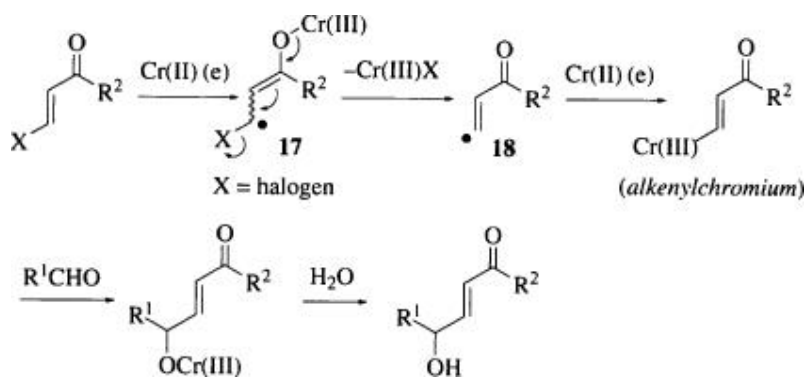
When an  $\alpha$ ,  $\beta$ -unsaturated ketone is treated with chromium(II) in the presence of an aldehyde under strictly aprotic conditions, the generated chromium enolate **13** adds to the aldehyde, and successive one-electron reduction and intramolecular addition to the ketone group affords 2-(alkoxyalkyl)-substituted cyclopropanol **14** (Scheme 6, path A). The enolate **13** is easily protonated by replacing an aldehyde in path A with a trace amount of water to give cyclopropanol. (61, 62) The reaction course changes markedly when chlorotrialkylsilane is in the reaction mixture. Because of the fast trapping of the chromium enolate **13** with chlorotrialkylsilane,  $\gamma$ -siloxy allylic chromium compounds **15** are produced after the second one-electron reduction. These compounds add to aldehydes at the  $\gamma$ -position to afford cross pinacoltype coupling products **16** after desilylation.

**Scheme 6.**



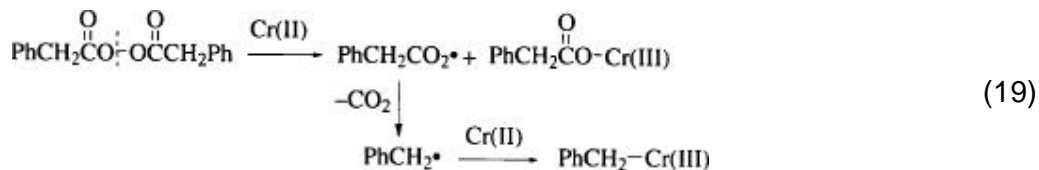
When a halogen atom is attached to the  $\beta$ -position of an  $\alpha, \beta$ -unsaturated ketone or ester, elimination of the halogen from the chromium enolate **17** gives the alkenyl radical **18** having a ketone or ester group at the  $\beta$ -position (Scheme 7). One-electron reduction of the radical **18** generates the corresponding alkenylchromium species. Therefore, in this case, a catalytic amount of nickel salt is not necessary for the preparation of alkenylchromium compounds from such alkenyl halides (See the [Scope and Limitations](#) section). (63)

**Scheme 7.**



#### 2.4. Reduction of Hetero-Hetero or Hetero-Carbon Bonds

Treatment of peroxides with chromium(II) causes reductive cleavage of the oxygen-oxygen bond to generate alkoxychromium(III) compounds (Eq. 19). (2)

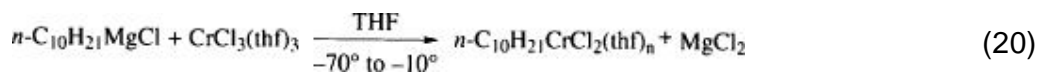


Azides are reduced to amines with chromium(II) with evolution of nitrogen gas. (64-66)

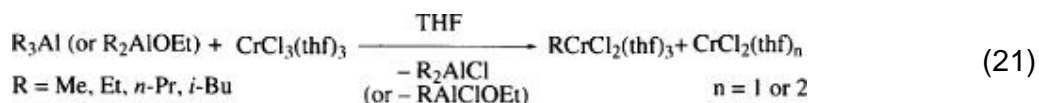
Carbon-oxygen bonds of sulfonates and allylic or propargylic phosphates, or phosphates at the  $\alpha$ -position of a carbonyl group are cleaved with chromium(II). (18, 67) Similarly, nitrogen-oxygen bonds of O-acetyl oximes are reductively cleaved with chromium(II). (68)

### 2.5. Transmetallation with Chromium(III) Halide

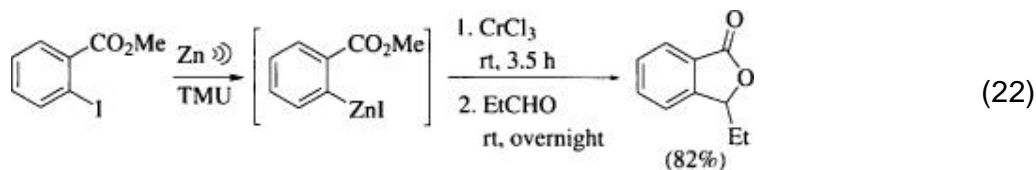
Organochromium compounds can be prepared by transmetallation from the corresponding organomagnesium compounds. (69-71) For example, *n*-decylchromium dichloride is prepared by treating 1 equivalent of trichlorotris(tetrahydrofuran) chromium(III) with 1 equivalent of *n*-decylmagnesium chloride in tetrahydrofuran (Eq. 20). (70, 71)



Similarly, a series of monoalkylchromium dichloride complexes with tetrahydrofurans as ligands,  $\text{RCrCl}_2(\text{thf})_3$ , are prepared by reactions of trichlorotris(tetrahydrofuran)chromium(III) with organoaluminum compounds in tetrahydrofuran (Eq. 21). (72) Chromium(II) chloride is formed by decomposition of the alkylchromium dichloride.



Transmetallation from arylzinc compounds also proceeds in the same manner (Eq. 22). (73)



Transmetalation of alkenyl groups from nickel(II) to chromium(III) is postulated in the preparation of alkenylchromium compounds under nickel catalysis. Without a nickel catalyst, alkenylchromiums are difficult to produce directly by reduction of haloalkenes with chromium(II) chloride. (10, 11)

Although it is not clear if direct transmetalation is involved in the cobaltcatalyzed preparation of alkylchromium reagents, (51) transmetalation of alkyl groups from a cobalt(III) dimethylglyoxime complex to chromium(II) in aqueous media proceeds smoothly (Eq. 23). (74, 75)



## 2.6. The Nature of Carbon-Chromium Bonds

### 2.6.1.1. Thermal Stability

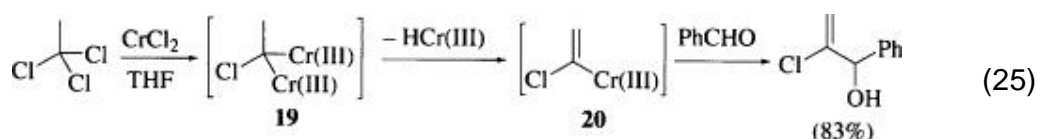
A series of monoalkylchromium complexes,  $\text{RCrCl}_2(\text{thf})_3$ , (70) can be prepared by transmetalation from alkylmagnesium or -aluminum compounds. The thermal stability of the complexes decreases in the order  $\text{Me} > \text{Et} > n\text{-Pr} > i\text{-Bu}$  both as solids and in tetrahydrofuran solution. (72) The activation energy for homolytic cleavage of the ethyl-chromium bond is estimated at 22 kcal/mol from the temperature dependence of the rate of decomposition of dichloro(ethyl)tris(tetrahydrofuran)chromium ( $\text{EtCrCl}_2(\text{thf})_3$ ) in tetrahydrofuran. (72) Solvated *n*-decylchromium dichloride is relatively stable at 0° in solution, undergoing slow homolysis at 20°, and rapid homolysis at 65° (Eq. 24). (76) The thermal decomposition of alkylchromium complexes releases alkanes, alkenes, and dimeric alkanes.



Electron-donating ligands such as pyridine increase the thermal stability of

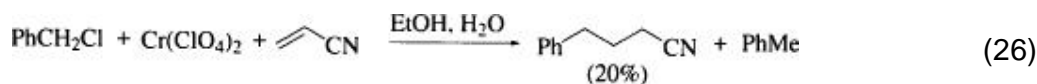
alkylchromium compounds. For example, stable pyridine-coordinated alkylchromium complexes are prepared by the ligand exchange of alkyl(dichloro)tris(tetrahydrofuran)chromium(III) with pyridine. (72, 77)

$\beta$ -Elimination from the geminal dichromium species **19** having a geminal chlorine atom proceeds rapidly, and the chloro-substituted alkenylchromium species **20** is produced (Eq. 25). (78, 79)

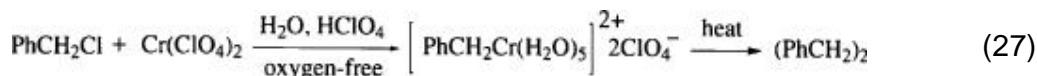


### 2.6.1.2. Hydrolysis

One-electron reduction of organic halides with chromium(II) gives carbon radicals, which are not sensitive to a proton source. Thus, carbon-carbon bond formation under aqueous conditions can proceed via the radical intermediates (Eq. 26). (2, 80-83)



Organochromium compounds react with water to give the corresponding hydrolysis products, although the hydrolysis of carbon-chromium bonds generated by successive one-electron reduction of the radicals proceeds slower than that of carbon-magnesium or -lithium bonds due to the covalent character of the carbon-chromium bonds. This feature derives from the slow exchange of ligands inside the coordination sphere of chromium(III). (72, 84-86) The rate of protonation depends on the amount of water and the presence of a halogen ion in the coordination sphere of chromium. (87, 88) For example, the half-life of the carbon-chromium  $\sigma$  bond increases to over 1.5 days under aqueous, oxygen-free conditions in the absence of a chloride ion in the coordination sphere of the alkylchromium(III) species. (87) An example of an organochromium compound with a very stable carbon-chromium  $\sigma$  bond was prepared and characterized by Anet and Leblanc using chromium(II) perchlorate (Eq. 27). (87, 89)

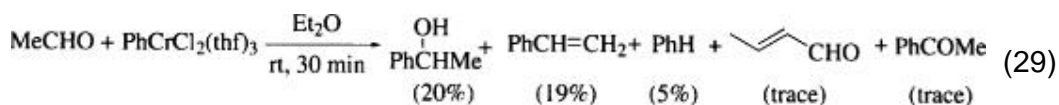
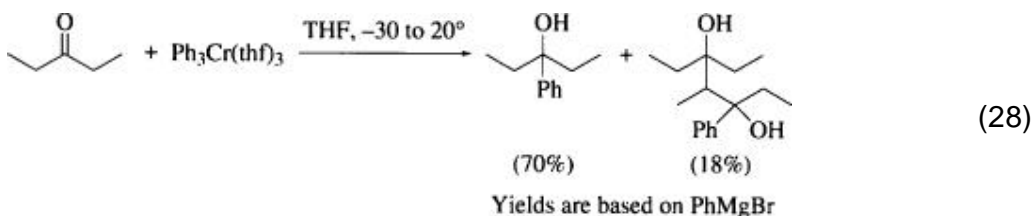




Sometimes, addition of a few equivalents of water does not disturb carbon-carbon bond formation with organochromium(III), allowing chromium-containing reactive species to be generated. (90, 91) There are also cases for which chromium-mediated reactions can be performed without protecting free hydroxyl groups. (71)

### 2.6.1.3. Nucleophilicity

Triphenyltris(tetrahydrofuran)chromium(III) is produced by transmetallation of phenylmagnesium bromide with chromium(III) chloride under aprotic conditions, (92, 93) and it reacts with carbonyl compounds to give a Grignard-type addition product. Two-to-one adducts, derived by aldol condensation and successive nucleophilic addition, are also obtained (Eq. 28). (94) Nucleophilic addition of phenyldichlorotris(tetrahydrofuran)chromium(III) to acetone as solvent takes place at room temperature to produce 2-phenyl-2-propanol in 71% yield together with mesityl oxide in 36% yield. In the reaction with acetaldehyde, nucleophilic addition and successive dehydration produces styrene along with the simple adduct 1-phenylethanol (Eq. 29). (95, 96)



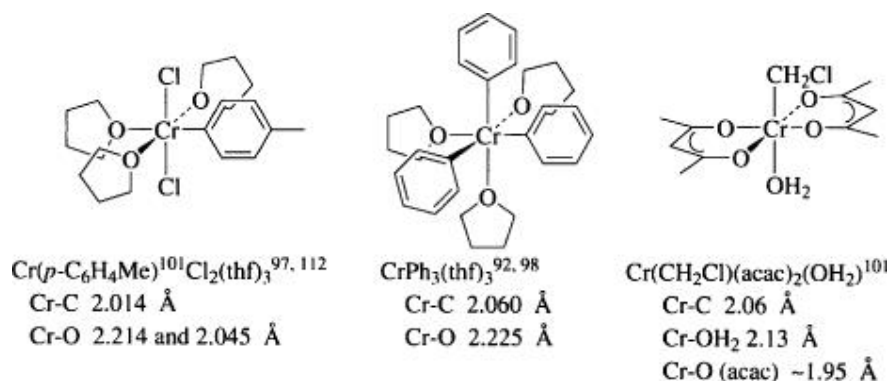
The reactivities of alkyl, allyl, alkenyl, and arylchromium species prepared by transmetallation and direct reduction are normally higher than those of the isolated organochromium compounds discussed above. This is probably due to the presence of Lewis acidic chromium(III) salts in the in situ prepared reaction system.

## 2.7. Structure of Organochromium Compounds

A number of mono-, di-, and triorganochromium(III) complexes have been prepared by the transmetallation or reduction methods, and their structures

determined by X-ray analysis. Several representative structures are shown in Figure 1. All have octahedral chromium(III) bound to the organic groups through a carbon-chromium  $\sigma$ -bond. The carbon-chromium bond distance varies between 2.01 and 2.11 Å, depending on the nature of the ligands trans to this bond. The carbon-chromium distance is close to 2.0 Å with a trans electronegative oxygen, (97, 98) and a trans nitrogen gives a carbon-chromium distance close to 2.1 Å. (99) The bonding in these complexes is therefore best described as a lone pair  $\sigma$  donation from a carbanion ligand to the chromium(III) cation, i.e.,  $\text{Cr(III)} \leftarrow \text{R}^-$ , and thus, these complexes are  $d^3$  octahedral complexes of the classical type. (100) Electron donor ligands such as tetrahydrofuran, dimethylformamide, and TMEDA effectively stabilize the chromium complexes.

Figure 1.



In general, the lengths of the chromium-carbon and -oxygen (102, 103) bonds are intermediate between those for boron(III) and tin(IV) compounds. Ligands on chromium can exert a steric influence on the transition state in some reactions, a typical example being the six-membered transition state in the reaction of an allylchromium reagent with a carbonyl compound, where regio- and stereoselectivity are observed (see below).

The molecular structures of triallylchromium, tris(2-methylallyl)chromium, and allylchromium dibromide were calculated using the Hartree-Fock (HF) and DFT methods. (104) Restricted HF geometries show some  $\sigma$ -character in the allyl bonding to metal centers, while the allyl groups coordinate in a pure trihapto fashion at the DFT level. Because the reactive species in solution could have solvent molecules such as DMF and THF in the coordination sphere, the structures of the reactive species that influence the allylic equilibrium are still unclear.

### 3. Scope and Limitations

#### 3.1. General Features of Organochromium Reagents

Because chromium(II) is a weaker reducing agent than other low-valent metals such as magnesium(0) and samarium(II), carbonyl compounds and even aldehydes can survive in the presence of chromium(II) ion. The reduction of organic halides with chromium(II) does not require the reagent activation that is needed with zinc and magnesium metals. The reduction can be conducted either by 1) adding the carbonyl compound to a solution of chromium(II) before addition of the organic halide or, 2) adding the chromium(II) salt to the mixture of the carbonyl compound and organic halide. The latter procedure is suitable for micro-scale reactions and intramolecular cyclizations.

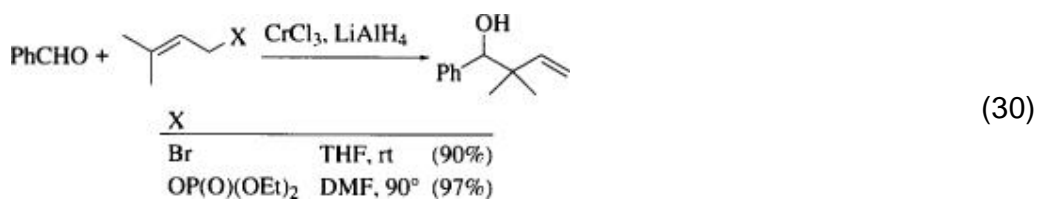
The Pauling electronegativity of chromium is 1.6, which is almost the same as that of titanium (1.5). Therefore, the nucleophilicity of organochromium reagents is not as great as for the corresponding organolithium or organomagnesium compounds. The bulk of the ligands on chromium also affects the nucleophilicity. These features enable the reagent to discriminate between the carbonyl groups of aldehydes and those of ketones or esters under usual conditions. In addition, it is possible to prepare organochromium compounds that contain such functional groups as ketones, esters, or nitriles. Because of the weak basicity of organochromium compounds, epimerization of a stereocenter  $\alpha$  to a carbonyl group is minimal. The allyl-, alkenyl-, and alkylchromium reagents discussed in the following section have these advantages. Organochromium reagents usually add to  $\alpha$ ,  $\beta$ -unsaturated aldehydes or ketones in a 1,2 fashion.

The chromium(III) ion has moderate Lewis acidity, and so the carbonyl oxygen can coordinate to it. This feature affects the geometry of the transition state of reactions of allylchromium reagents and also facilitates intramolecular cyclization by bringing the organochromium moiety and the carbonyl group into proximity.

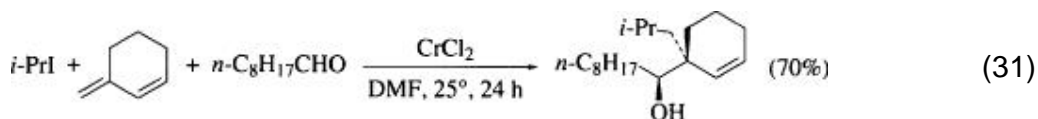
#### 3.2. Allylic Chromium Reagents

##### 3.2.1.1. Preparation

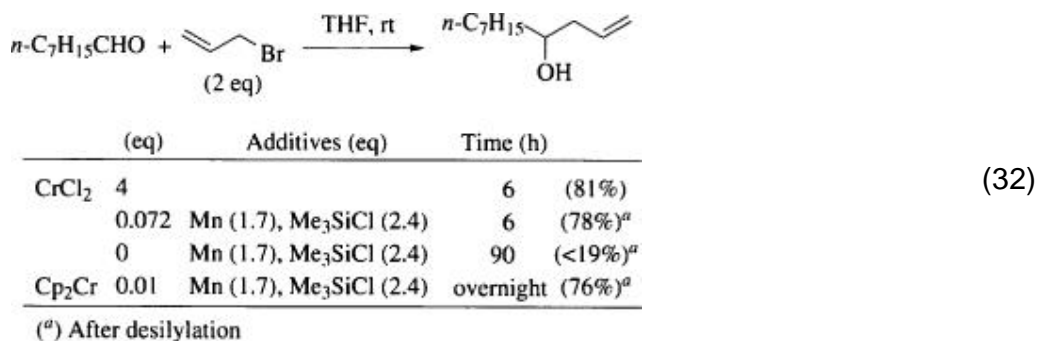
Allylic halides can be reduced in tetrahydrofuran or dimethylformamide with two equivalents of chromium(II) chloride or the low-valent chromium ion derived from two equivalents of chromium(III) chloride and one equivalent of lithium aluminum hydride in tetrahydrofuran. The resulting allylic chromium reagents easily dimerize to 1,5-dienes. (35) When the reduction is conducted in the presence of an aldehyde or a ketone, the allylic chromium reagents add to the carbonyl group to furnish homoallylic alcohols (Eq. 30). (5, 105) Allylic tosylates, (5) mesylates, (106) and diethylphosphates (18, 107) are also suitable precursors of the allylic chromium reagents (Eq. 30).



Another method for the preparation of allylic chromium compounds is the one-electron reduction of allylic radicals with chromium(II). Allylic radicals, which are intermediates in the direct reduction of allylic halides with chromium(II), can also be generated by 1) addition of radicals to 1,3-dienes, or 2) homolytic cleavage of allylic cobalt(III) species. (90) In the first method, treatment of tertiary or secondary alkyl iodides with chromium(II) in DMF generates the corresponding alkyl radicals by one-electron reduction. Therefore, when the one-electron reduction of alkyl radicals is conducted in the presence of a 1,3-diene and an aldehyde, three-component addition occurs via the allylic radical and chromium compound (Eq. 31). (50)



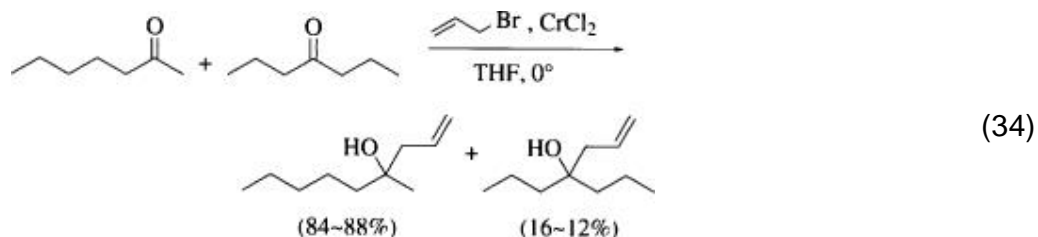
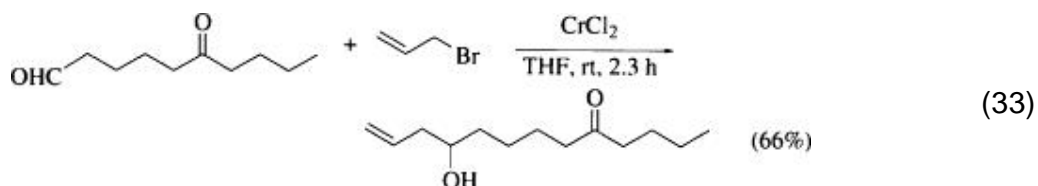
Chromium(II) can be used in catalytic quantities by adding manganese metal as a reductant and chlorotrimethylsilane to promote chromium-oxygen to silyl transfer (Eq. 32). (44) Either chromium(II) or chromium(III) can be used as the catalyst at the start of the reaction. Furthermore, the catalytic efficiency of the chromium center is enhanced by using chromocene (Cp<sub>2</sub>Cr) as a precatalyst. (44)



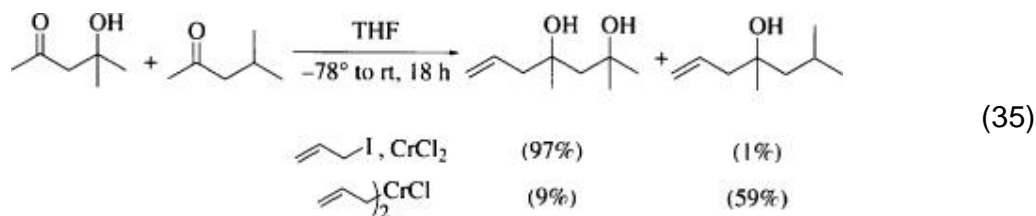
Several attempts to regenerate chromium(II) with a zinc or sodium amalgam in tetrahydrofuran have been reported, but with limited success. (43)

### 3.2.2. Functional Group Selectivity

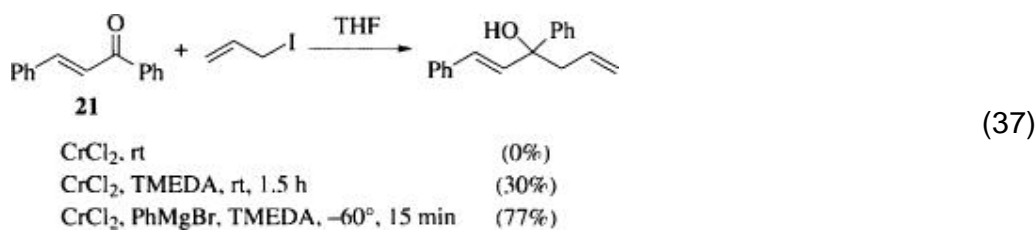
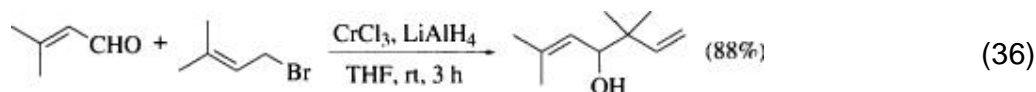
Although allyl chromium reagents also add to ketones to give homoallylic alcohols, ketones are less reactive than aldehydes. Accordingly, selective addition to aldehydes can be accomplished (Eq. 33). (5) In addition, the allylchromium reagent discriminates between the two ketone groups of heptan-2-one and heptan-4-one with a selectivity of 84–88% (Eq. 34). (5) The following functional groups are also tolerated under the usual reaction conditions: ester, lactone, amide, nitrile, alkyne, olefin, 1,3-diene, conjugated enyne, chloride, and acetal. A hydroxy group can be protected as OAc, OBn, OTBDMS, OTBDPS, OMOM, OCH<sub>2</sub>OBn, or OCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>OMe-*p* (OPMB).



The reaction of organochromium reagents with carbonyl compounds is occasionally accelerated by addition of 1-3 equivalents of water or ethanol. Chemoselective addition of an allyl group to a  $\beta$ -hydroxyketone by using this chelation-accelerating effect is observed (Eq. 35). (108, 109) In contrast to the allylchromium compound derived by reduction of allyl iodide with chromium(II) chloride, the diallylchromium reagent prepared from 2 equivalents of allylmagnesium bromide and chromium(III) chloride shows reverse chemoselectivity which could stem from a non-chelated transition state. (109, 110)

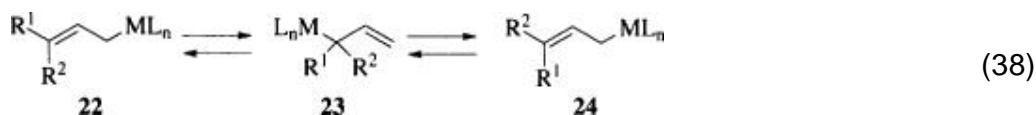


Allylchromium reagents add to  $\alpha$ ,  $\beta$ -unsaturated aldehydes in a 1,2 fashion (Eq. 36). (105)  $\alpha$ ,  $\beta$ -Unsaturated ketones like chalcone (**21**) do not cleanly give the corresponding allyl adduct. (105) However, the chromium(II) complex derived by treating chromium(II) chloride with phenylmagnesium bromide efficiently adds to enones (Eq. 37). (111) This homogeneous reaction proceeds even at  $-60^\circ$ .



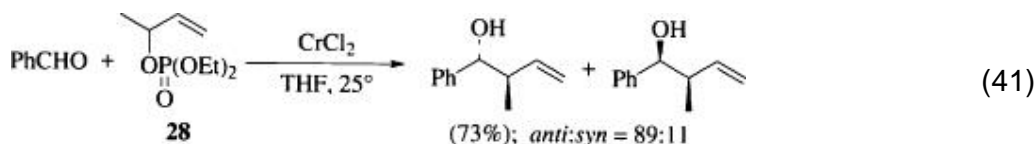
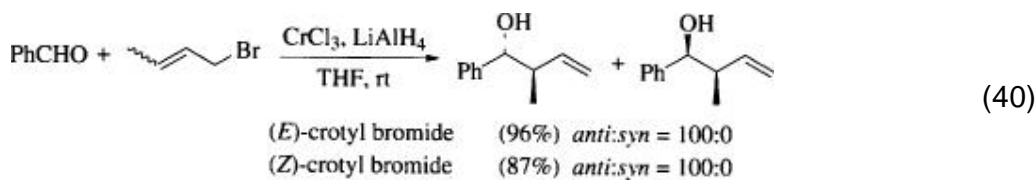
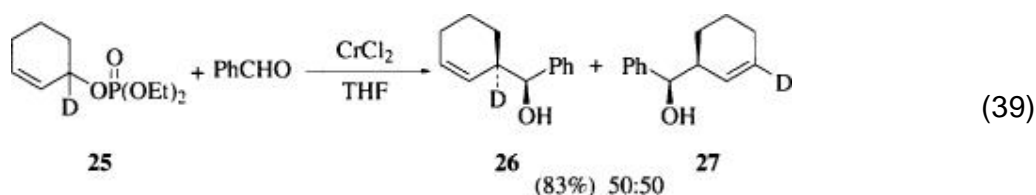
### 3.2.2.1. Allyl Chromium Equilibration

Although the  $\eta^1$  or  $\eta^3$  structure of reagents derived from an allylic halide and chromium(II) chloride is not clear, it is likely to be  $\eta^1$  at least in the transition state of the reaction with carbonyl compounds. Equilibration between three isomeric allylic metal compounds **22–24** can occur to cause E/Z isomerization (Eq. 38). The rate of equilibration depends on the nature of the



allylic metal compounds: it is fast with allylic lithium and magnesium compounds and slow with allylic boron compounds. Equilibration of allylic

chromium compounds is fast at room temperature except for  $\gamma$ -disubstituted allylic chromium compounds. (107) For example, treating 1-*d*-2-cyclohexenyl phosphate (25) and benzaldehyde with chromium(II) chloride in tetrahydrofuran gives two regioisomeric alcohols 26 and 27 in a 50:50 ratio (Eq. 39). (18) Because of the steric interaction between ligands on chromium and the substituents on the allyl fragment, the equilibrium lies toward the allylic chromium species with less steric crowding of the carbon-chromium bond. Moreover, allylic metal compounds normally react with carbonyl compounds at the  $\gamma$  position of the allylmetal unit. Thus, reactions between prenyl halides and aldehydes afford 3,3-dimethyl substituted homoallylic alcohols. The reaction of crotyl bromide and benzaldehyde mediated by chromium(III) chloride and lithium aluminum hydride in tetrahydrofuran gives an anti adduct with high diastereocontrol regardless of the configuration of the crotyl bromide (Eq. 40). (6, 112) The allylic chromium reagent derived from reduction of but-3-en-2-yl diethylphosphate (28) with chromium(II) chloride also gives the same anti adduct as the major product (Eq. 41). (18)



These results suggest that addition to aldehydes takes place via the same intermediate, probably the *E* crotylchromium reagent, which could be the most stable and/or reactive of the three isomeric crotylchromium compounds in fast equilibration. Indeed, the reaction with 2-cyclohexenyl phosphate furnishes the *syn* adduct stereoselectively (Eq. 39). (18) In the reaction between allylic

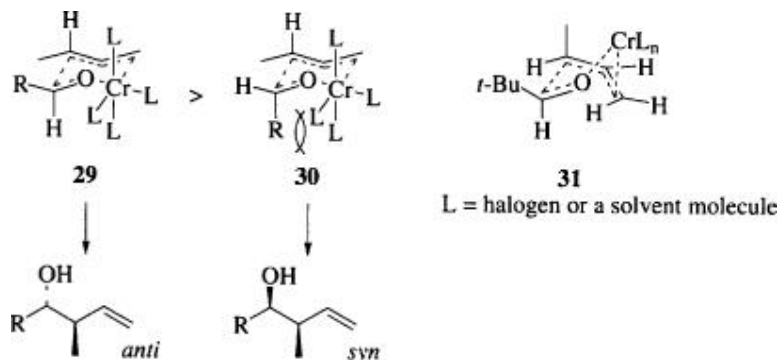
chromium reagents [ $R^1CH = CHCH_2Cr(III)$ ] and aldehydes ( $R^2CHO$ ), the stereochemistry of the allylic chromium reagent and not the allylic halide determines the configuration of the major product.

### 3.2.2.2. 1,2-Diastereoselectivity

The addition of crotylchromium compounds to aldehydes yields mainly the anti addition products regardless of the geometry of the crotyl bromide (Eq. 40). (6, 112) This observation suggests that the crotylchromium reagent prepared in situ equilibrates to the more stable and/or more reactive E isomer.

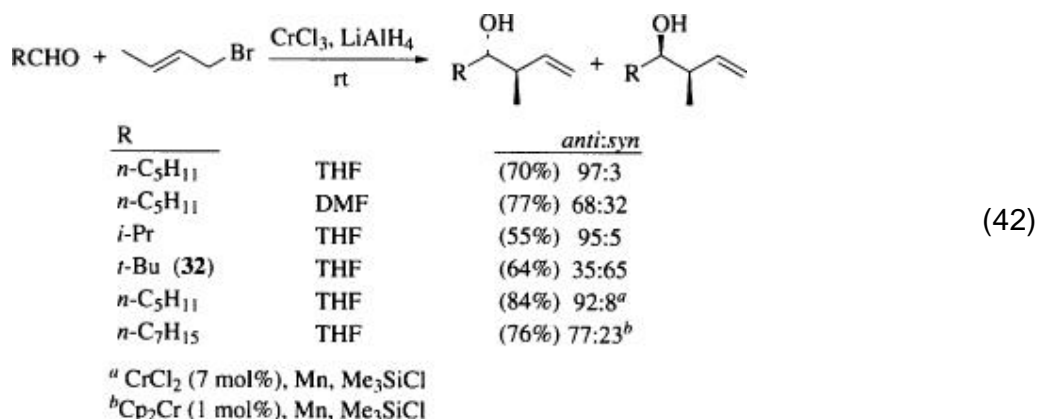
Chromium(III) complexes prefer an octahedral configuration in which the coordination sphere is often supplemented with solvent molecules such as tetrahydrofuran. (97, 98, 113) Ligand displacement in the octahedral E crotylchromium complex by the aldehyde generates a cyclic six-membered transition state. In the absence of any additional stabilization, a chair-form cyclic transition state is more favorable than a boat form. Two idealized chair-form six-membered transition states **29** and **30** for the reaction of E crotylchromium are shown in Scheme 8. (6, 112) The anti selectivity in the addition of crotylchromium reagents to aldehydes is explained by the Zimmerman-Traxler six-membered transition state **29**, in which both the methyl group and R occupy equatorial positions. The diastereoselectivity stems from different steric interactions between R and the aldehydic hydrogen with ligands on chromium(III).

Scheme 8.



As the aldehyde substituent R becomes larger, higher diastereoselectivities are obtained (Eq. 42). (44, 112) One exception, however, is 2,2-dimethylpropanal (**32**,  $R = t\text{-Bu}$ ), where the syn diastereomer is the main product. This result is explained by preference for the skew-boat-like transition state **31** because of the severe gauche interaction between the *tert*-butyl and methyl groups in **29**.





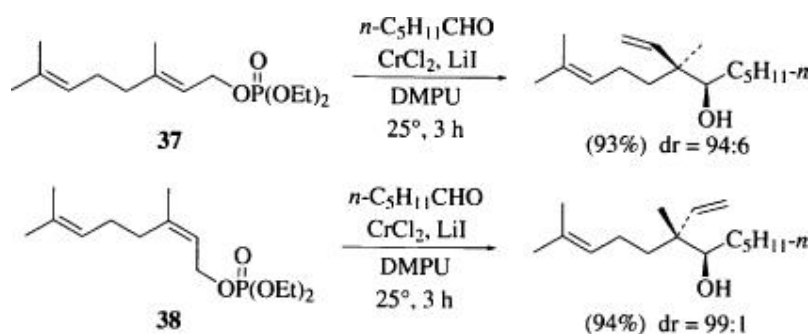
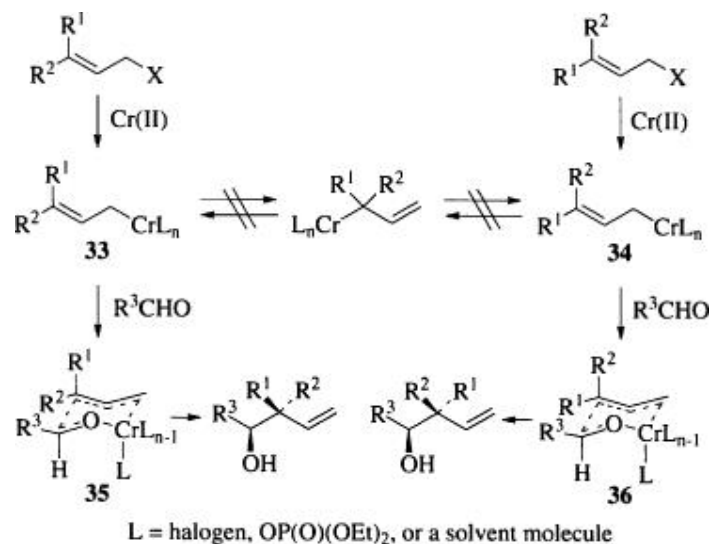
The diastereoselectivity depends on the solvent, and the reaction has lower selectivity in dimethylformamide than in tetrahydrofuran. Strong coordination of dimethylformamide to chromium(III) could interfere with the formation of a tight six-membered transition state.

High selectivity is also observed with a combination of a catalytic amount of chromium(II) chloride, manganese, and chlorotrimethylsilane in THF. However, the anti/syn ratio decreases when a chromocene catalyst is employed. (44)

### 3.2.2.3. Substituted Allylic Systems

The presence of two substituents at the  $\gamma$  position of an allylic metal system retards the allylic equilibration of Eq. 38. (114) If equilibration of the intermediate allylic chromium reagents is slow relative to the addition to the aldehyde, then the two stereoisomeric allylic chromium reagents **33** and **34** should react via the two diastereomeric transition states **35** and **36**, respectively (Scheme 9). The phenomenon is observed in the reaction of  $\gamma$ -disubstituted allylic phosphates **37** and **38** with aldehydes mediated by chromium(II) chloride and a catalytic amount of lithium iodide in *N,N*-dimethylpropyleneurea (DMPU) (Eq. 43). (107, 115)

**Scheme 9.**



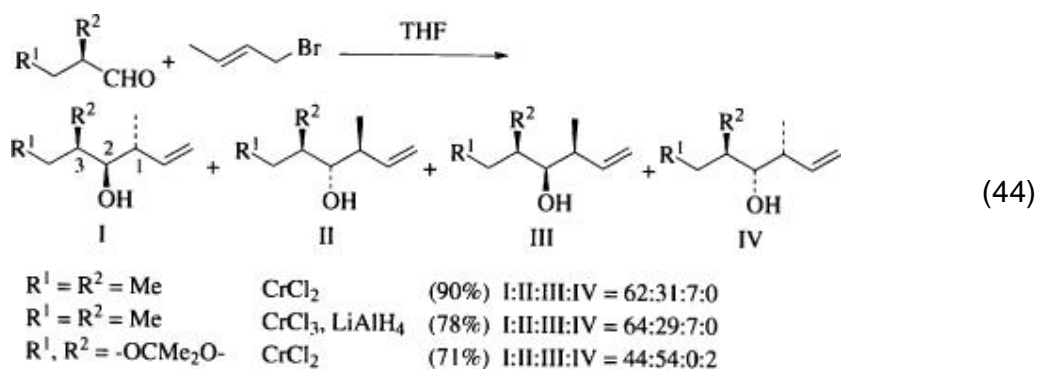
(43)

### 3.3. Aldehyde Diastereofacial Selectivity (Cram- and anti-Cram Addition)

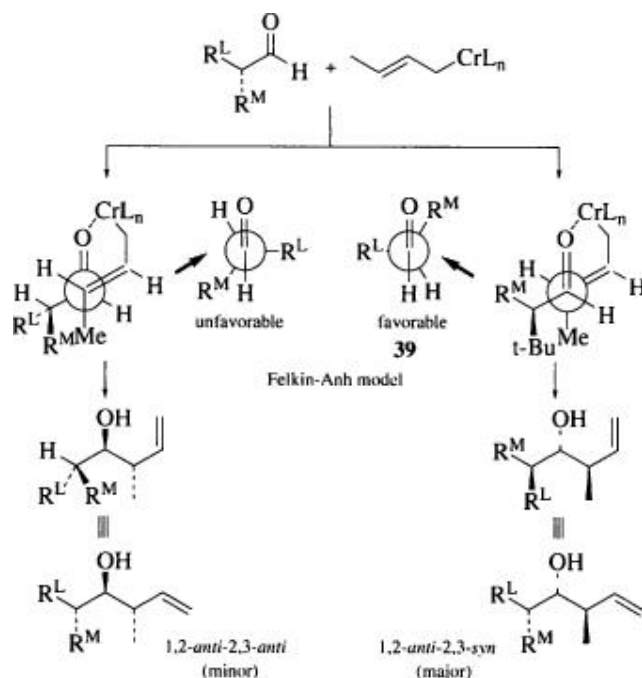
Allylation of aldehydes with allylic chromium reagents usually proceeds without epimerization at the  $\alpha$  position because of the low basicity of the reagent.

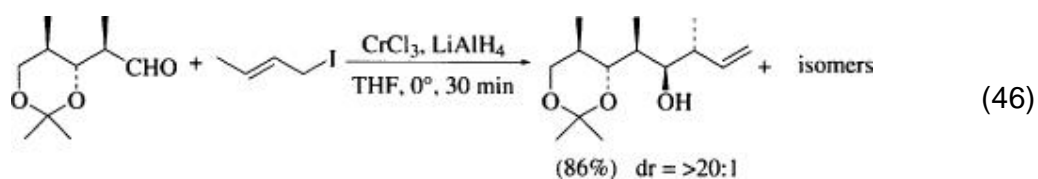
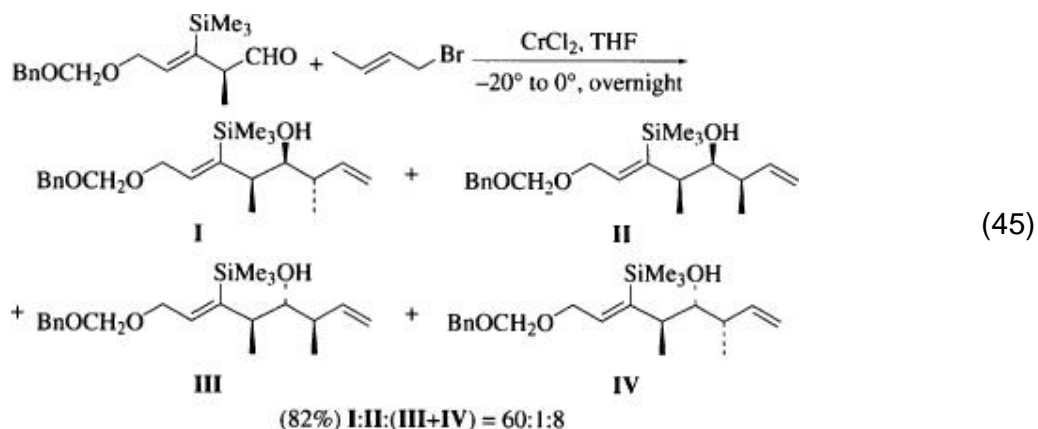
Addition of crotylchromium to aldehydes bearing a stereogenic center  $\alpha$  to the carbonyl group can provide four diastereomers. Here, the problem of aldehyde diastereofacial selectivity (Cram and anti-Cram selectivity) arises in addition to the 1,2-syn,anti selectivity issue associated with the carbon-carbon bond-forming event. In contrast to the excellent anti selectivity at the 1,2 positions, selectivity at the 2,3 positions (the Cram / anti-Cram ratio) is only moderate in many cases (Eq. 44). (112, 116) Large substituents at the  $\alpha$  carbon lead to predominant stereoisomers with the 1,2-anti, 2,3-syn configuration. This orientation is consistent with the Felkin-Anh modification **39** (117, 118) of Cram's rule (Scheme 10). The diastereomeric ratios at the 2,3 position vary and the controlling factors concerning the influence of the aldehyde structure on the diastereoselectivity are not clear. Acyclic aldehydes

with protected  $\beta$ -hydroxy groups tend to have ratios in the range 1.6:1 ~ 1:1, and the ratios are not sensitive to either solvent or the type of protecting group. (119) These results suggest that chelation is not important. High 2,3-diastereoselectivity is obtained with aldehydes having large substituents (Eq. 45), (120, 121) especially a cyclic acetal group on the  $\beta$  carbon (Eq. 46). (119, 122) In addition, the 2,3-syn selectivity is enhanced with aldehydes that bear a syn dimethyl arrangement at the C-2 and C-4 carbons. However, the selectivity illustrated in Eq. 46 is dependent on the configuration of the aldehyde substrate.

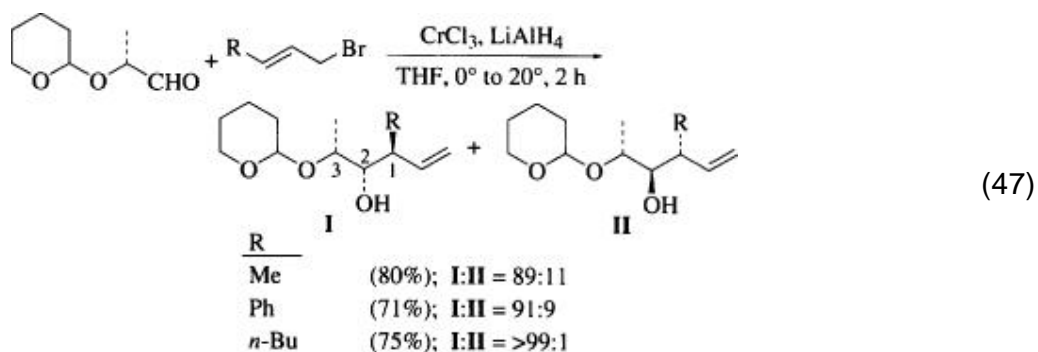


Scheme 10.



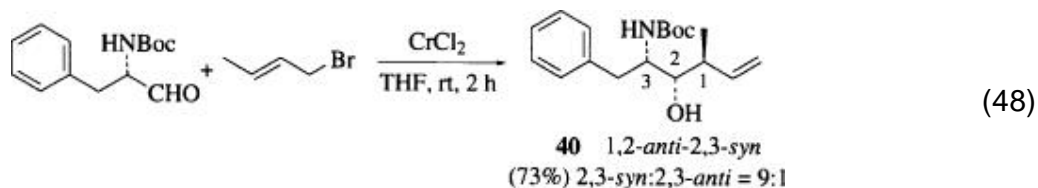


The structure of the allylic chromium reagent also affects the 2,3-diastereoselectivity. The 2,3-syn selectivity increases with increasing size of the  $\gamma$  substituent R of the reagent (Eq. 47). (123) This result is consistent with the Felkin-Anh model (Scheme 10).



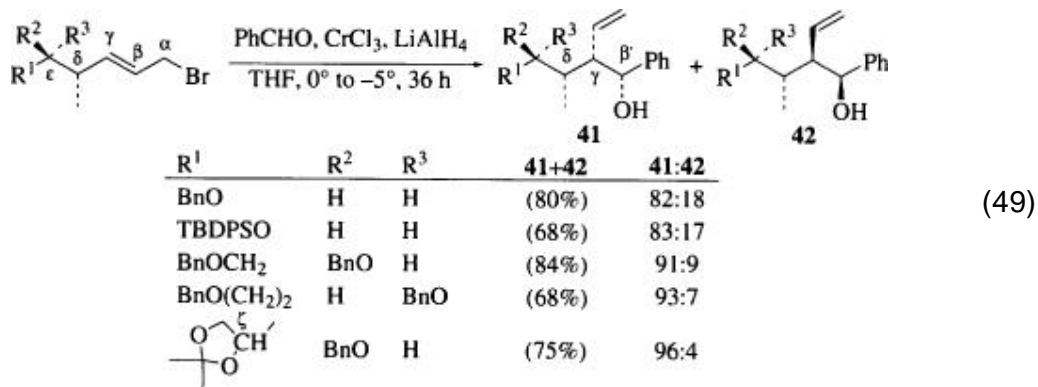
When an amino group is present at the  $\alpha$ -position of an aldehyde, the Cram- and anti-Cram selectivity varies with the amino protective group. In the reactions with allylchromium reagents, the addition to an aldehyde is not stereoselective except when the amino group is protected with bulky groups. In this case, 2,3-anti-selectivity is observed. (124, 125) Addition of a

crotylchromium reagent to an aldehyde, however, results in high 2,3-syn selectivity when one of the amino hydrogens is unprotected, and the 1,2-anti-2,3-syn adduct **40** is produced (Eq. 48). (124)

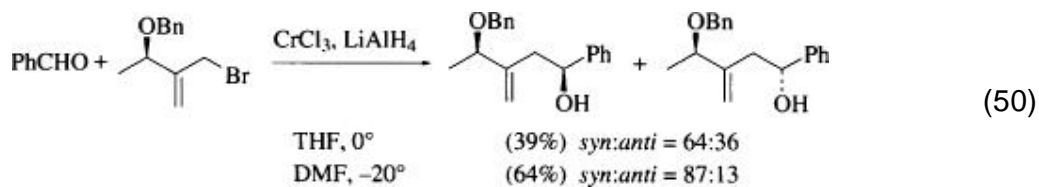


### 3.3.1.1. Chiral Allylic Chromium Reagents

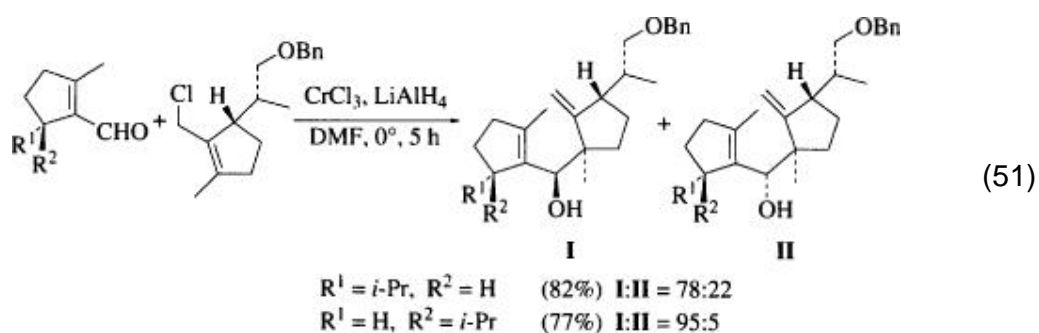
Reaction of acyclic chiral allylic bromides with aldehydes gives two adducts **41** and **42** with moderate to high diastereofacial control (Eq. 49). (126) The principal adducts have an all-syn arrangement of the  $\beta$ -hydroxy,  $\gamma$ -vinyl, and  $\delta$ -methyl substituents. The stereogenic center at the  $\delta$  carbon of the allylic halide determines the configuration of the stereocenters created at the  $\gamma$  and  $\beta'$  positions of the products. The selectivity is also in accord with the transition state shown in Scheme 10. Additional stereocenters at  $\epsilon$  and  $\xi$  carbons of the allylic bromides increase the diastereoselectivity because of the increase in the effective size of  $R^L$  (large group).



When siloxy (127) or alkoxy groups (128, 129) are attached to the C(2) position of allylic chromium compounds, 1,4-induction is reported. The selectivity of Eq. 50 is explained by 1,3-allylic strain in the six-membered chair-form transition state. (128, 129)

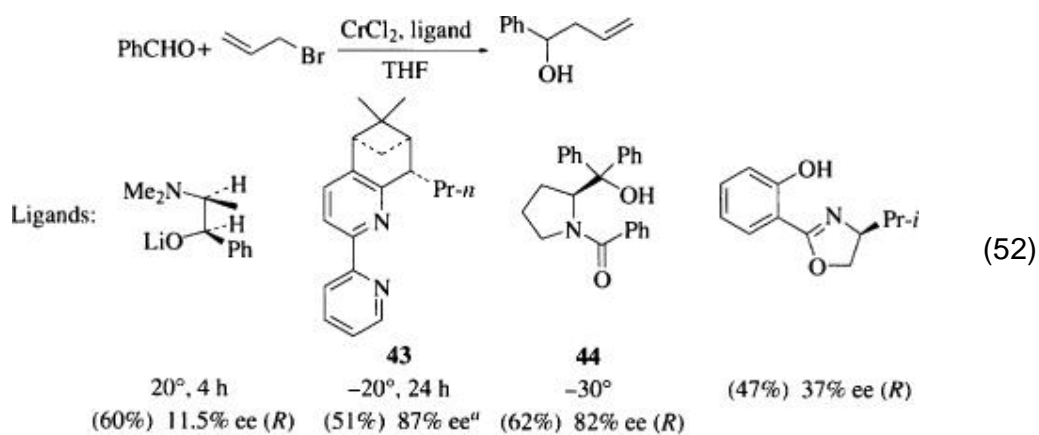


Double stereodifferentiation is observed in the reaction of chiral aldehydes with chiral allylic halides mediated by chromium(II) chloride (Eq. 51). (126, 130, 131)



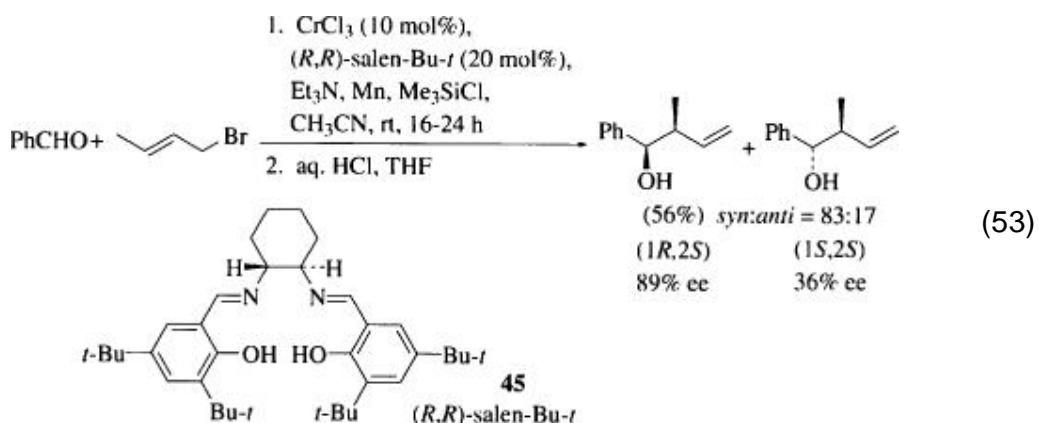
### 3.3.1.2. Enantioselective Addition with Chiral Ligands

The addition of allylic chromium reagents to aldehydes in the presence of some chiral bidentate ligands gives moderate asymmetric induction (Eq. 52). (132) A good level of asymmetric induction is obtained when a chiral 2,2'-dipyridyl **43** or amino alcohol type ligand **44** is employed. (133, 134)



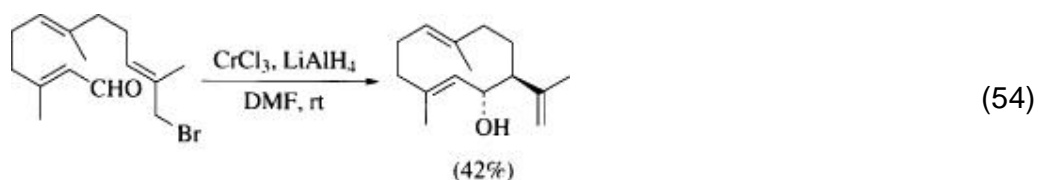
<sup>a</sup>The absolute configuration was not established.

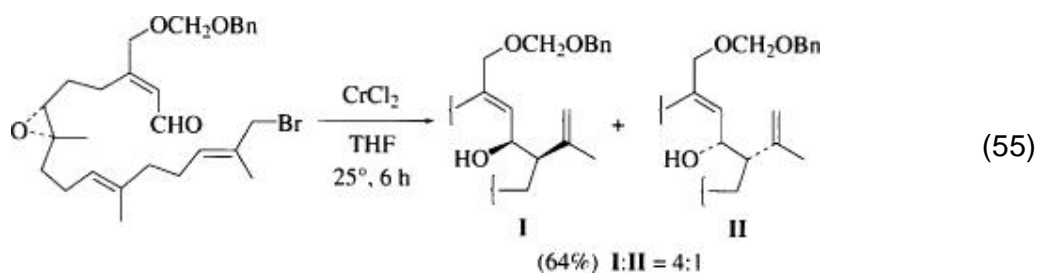
A catalytic asymmetric reaction is achieved with 10 mol% of a chromium-salen complex **45**, using manganese as a reductant. (16) The syn/anti selectivities of the reactions between crotylchromium species and aryl aldehydes depend on the salen ligand used, and syn adducts are produced predominantly when 2 equivalents of the salen ligand are used based on chromium(II) (Eq. 53). (135-137) The selectivity is explained by an acyclic transition state containing two chromium-salen complexes.



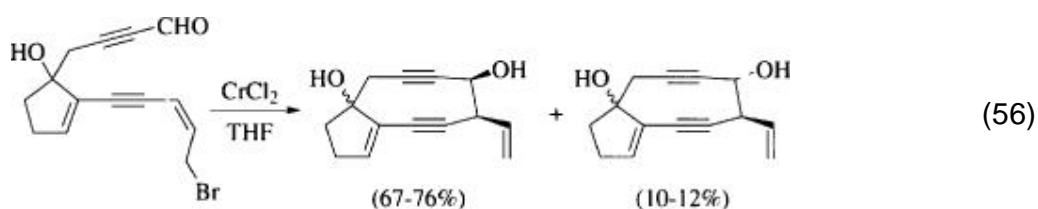
### 3.3.1.3. Intramolecular Cyclization

Because the chromium-mediated coupling reaction of allylic halides and aldehydes proceeds under mild conditions with high 1,2-diastereoselectivity, it has been used to effect intramolecular cyclization to give medium-sized (Eq. 54) (106, 138-140) and large (Eq. 55) rings. (141-145) These cyclizations proceed with high 1,2-anti selectivity. Macrocyclization proceeds with moderate to high stereocontrol, owing to the influence of the remote asymmetric centers on the transition state.

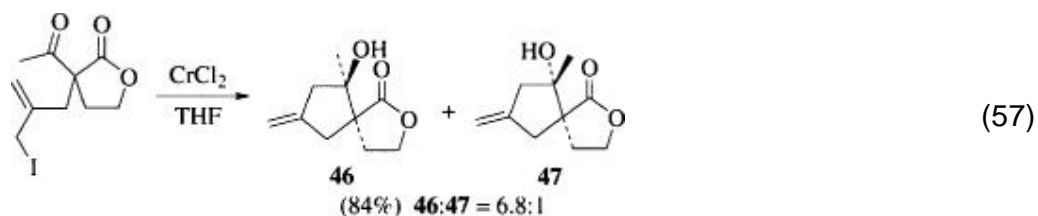




Because of the moderate Lewis acidity of chromium(III), labile hydroxy groups survive during the carbon-carbon bond formation (Eq. 56). (140, 146)



The intramolecular reaction of allylic halides with 2-acetoxybutyrolactone provides two products (**46** and **47**), with the spirocyclic product **46** resulting from chelation control predominating (Eq. 57). (147) The diastereomer ratio is essentially the same as that obtained with samarium(II) iodide and magnesium.



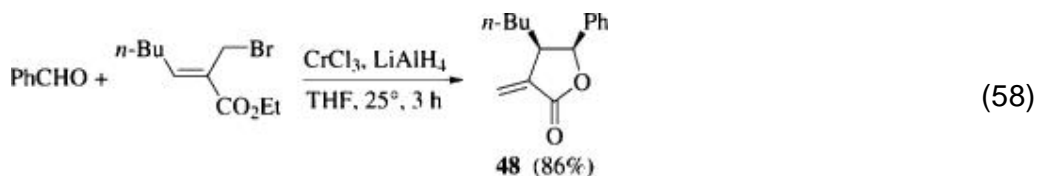
#### 3.3.1.4. Functionalized and Heterosubstituted Allylic Chromium Reagents

When functionalized allylic halides are used as precursors of allylic chromium reagents, an acyclic molecule functionalized for further manipulation is produced. In addition, the internal coordination of heteroatoms sometimes fixes the conformation of the intermediate allylic chromium species and consequently, high diastereoselectivity may arise.

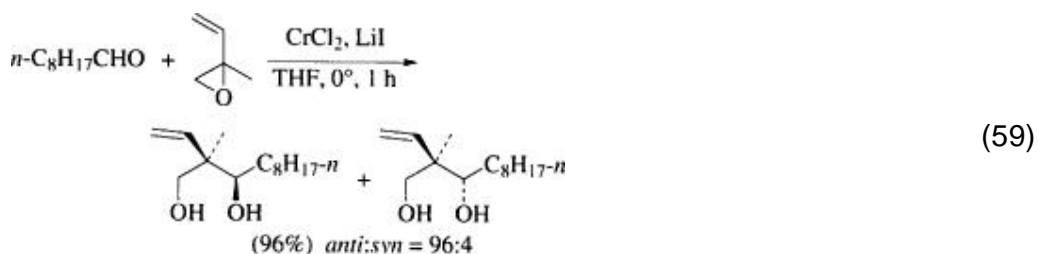
The reaction of  $\alpha$ -bromomethyl- $\alpha$ ,  $\beta$ -unsaturated esters with aldehydes



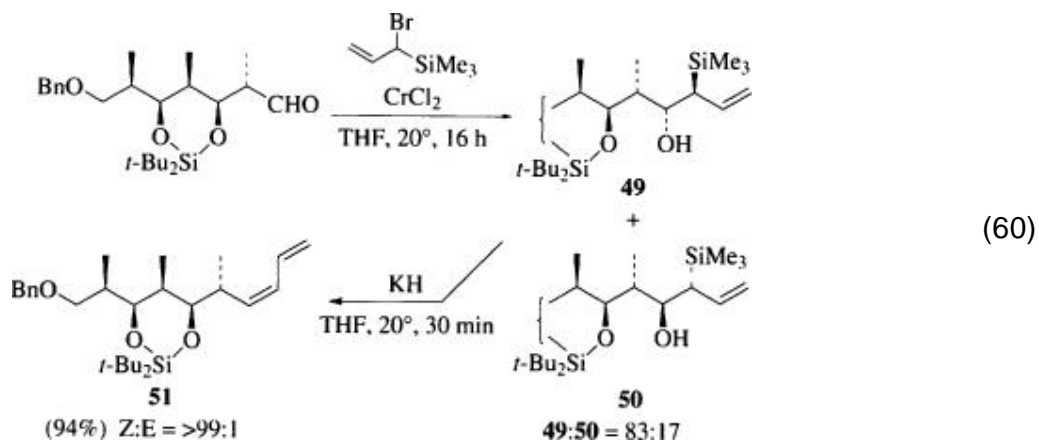
mediated by chromium(II) chloride (or chromium(III) chloride-lithium aluminum hydride) affords homoallylic alcohols, which cyclize to yield  $\alpha$ -methylene- $\gamma$ -lactones **48** in a stereoselective manner (Eq. 58). (148, 149) The reaction between  $\alpha$ -bromomethyl- $\alpha$ ,  $\beta$ -unsaturated sulfonates and aldehydes also proceeds with high stereocontrol. (150, 151)



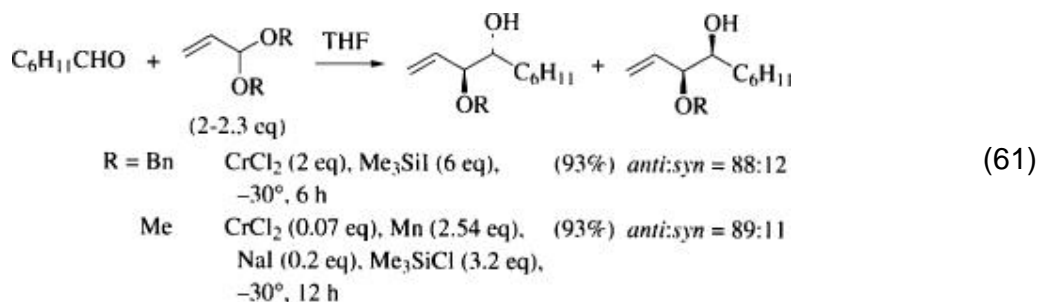
Vinyl-substituted  $\beta$ -hydroxy allylchromium reagents are produced by reduction of 1,3-diene monoepoxides with chromium(II) chloride in the presence of lithium iodide. These reagents react with aldehydes stereoselectively to give ( $R^*$ ,  $R^*$ )-1,3-diols having a quaternary center at C2 (Eq. 59). (152)



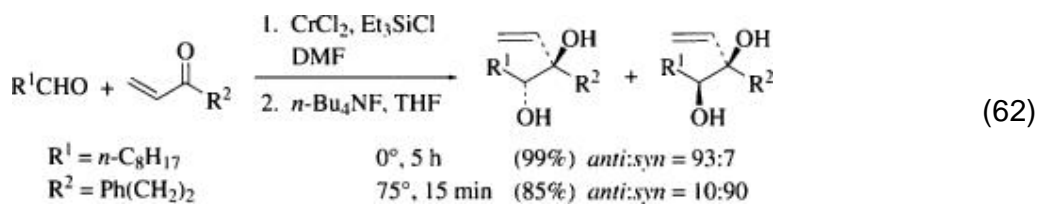
A trimethylsilyl-substituted allylchromium reagent can be prepared by treating either 1-trimethylsilyl-3-bromopropene or 3-trimethylsilyl-3-bromopropene with chromium(II) chloride. This reagent reacts with aldehydes at room temperature to yield exclusively anti- $\beta$ -hydroxysilanes **49** and **50**. (153) These adducts can be converted smoothly into *Z* terminal dienes **51** by a Peterson syn elimination with potassium hydride (Eq. 60). (154-157)



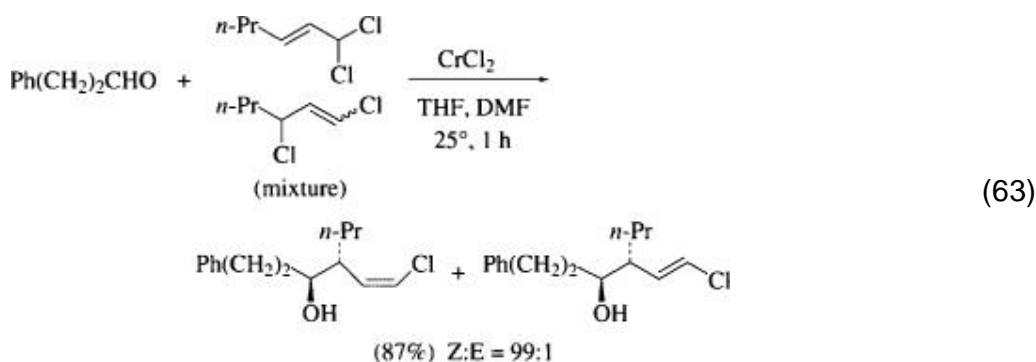
In situ reduction of acrolein dialkyl acetals with chromium(II) chloride in tetrahydrofuran provides  $\gamma$ -alkoxy-substituted allylic chromium reagents, which add to aldehydes to afford 3-buten-1,2-diol derivatives. The reaction rate and stereoselectivity are increased by adding iodotrimethylsilane (Eq. 61). (158-160) By using manganese as a reductant, a catalytic version of this reaction using a chromium(II) salt can also be achieved. (161) In situ formation of  $\alpha$ - and  $\gamma$ -alkoxy-substituted allyl iodides with iodotrimethylsilane is postulated.



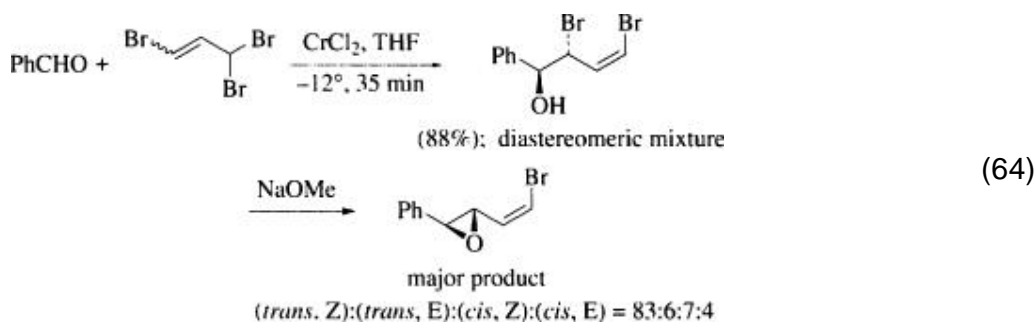
$\gamma$ -Siloxysubstituted allylic chromium reagents are generated by electron transfer to  $\alpha$ ,  $\beta$ -unsaturated ketones with chromium(II), trapping of the intermediate with chlorotrimethylsilane, and further one-electron reduction. The anti:syn ratio of the reaction depends markedly on the reaction temperature (Eq. 62). (162)



A mixture of 3-alkyl-substituted 1,1-dichloro-2-propene and 1,3-dichloro-1-propene is reduced with chromium(II) chloride to give an  $\alpha$ -chloroalkylchromium reagent, which reacts with aldehydes to produce a 2-substituted *anti*-(*Z*)-4-chloro-3-buten-1-ol in a regio- and stereoselective manner (Eq. 63). (163)

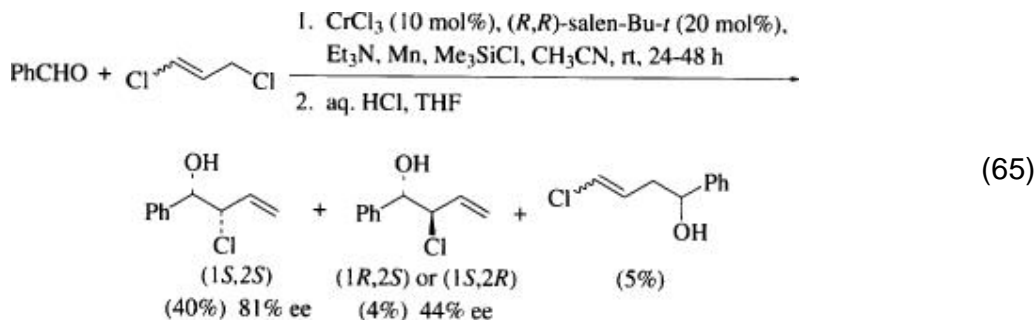


Reaction of 1,3,3-tribromopropene with chromium(II) chloride in the presence of benzaldehyde, followed by treatment of the initial product with sodium methoxide affords the *trans*, *Z* adduct selectively (Eq. 64). (164)



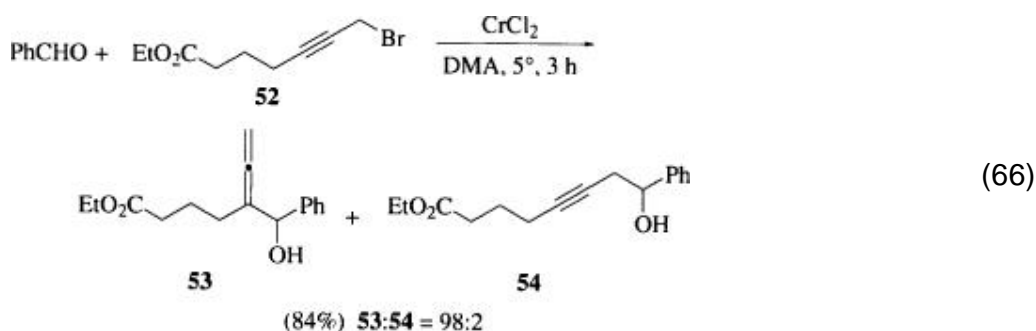
When using the chromium chiral salen system, aryl-substituted syn chlorohydrins are produced in moderate yields (Eq. 65). (165) The

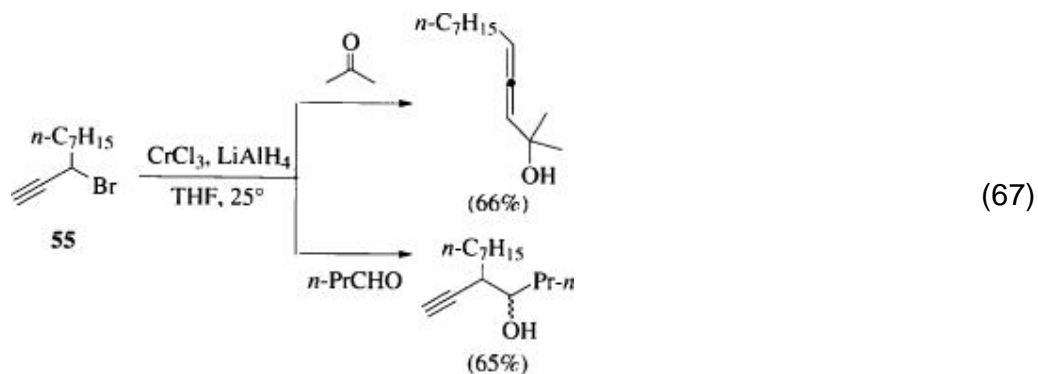
enantiomeric excess of the syn chlorohydrins is 61–83%. The chlorohydrin can be converted into cis vinylepoxides upon treatment with a suitable base.



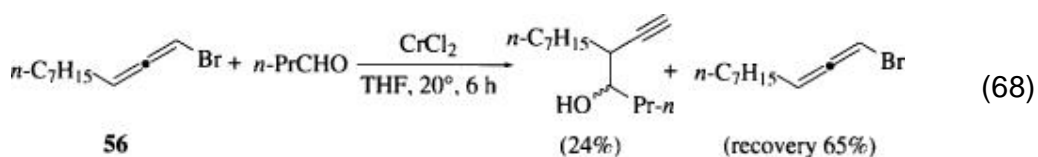
### 3.3.1.5. Propargylic Chromium Reagents

Propargylic halides react with carbonyl compounds in the presence of chromium(II) chloride or a combination of chromium(III) chloride and lithium aluminum hydride to give a mixture of allenic and homopropargylic alcohols. (166, 167) The selectivity of the reaction depends on the substitution of the propargylic halide, the structure of the carbonyl compound, and the presence of hexamethylphosphoric triamide in the mixture. For example, organochromium reagents, derived from primary propargylic halides **52** with a substituent at the acetylenic carbon, react with carbonyl compounds to afford allenic alcohols **53** accompanied by only small amounts of homopropargylic alcohols **54** (Eq. 66). (166-168) When secondary propargylic halides **55** are used, the product distribution depends on the carbonyl compound (Eq. 67). (167) Adding hexamethylphosphoric triamide as a cosolvent increases the amount of allenic products.

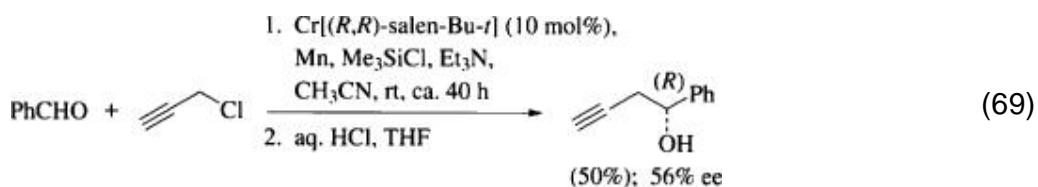




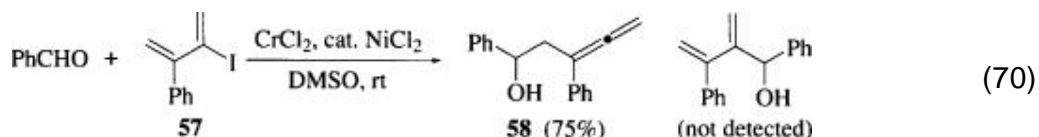
Allenyl bromide **56** is not reduced smoothly under the same reaction conditions as propargylic bromides, but the allenic chromium reagent nevertheless reacts with an aldehyde to give the same distribution of products as the reaction between the corresponding propargylic bromide and the aldehyde (Eq. 68). (167)



Asymmetric addition is accomplished with a moderate enantiomeric excess by using the chromium-salen complex and manganese system (Eq. 69). (169)



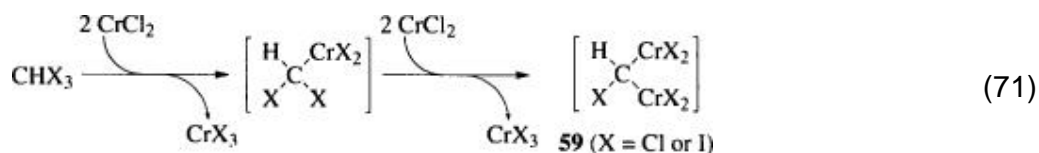
When a 2-iodo-1,3-diene derivative **57** is treated with chromium(II) and nickel (II) (see below), two reactions can occur (Eq. 70), (170) but only the allenic compound **58** is produced by carbon-carbon bond formation at the terminal diene carbon. (170, 171)



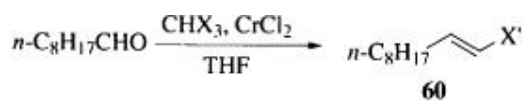
### 3.4. Geminal Dichromium Reagents

#### 3.4.1.1. Generation and Reactivity

Chromium(II) chloride reduces two of the three halogens of haloform ( $\text{CHX}_3$ ) to form geminal dichromium reagents **59** (Eq. 71). (8) Since chromium(II) is a one-electron reductant, four equivalents of chromium(II) are required based on the haloform. The second reduction of halogen leading to the geminal dichromium reagents **59** proceeds faster than the first step.

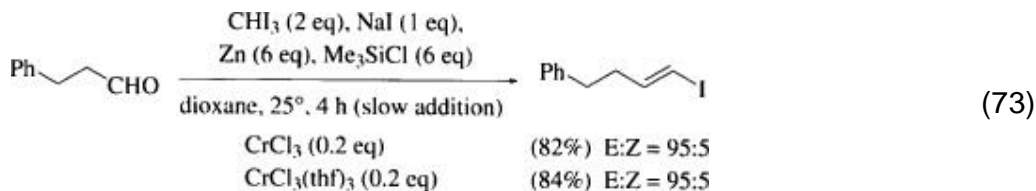


The geminal dichromium reagents prepared from iodoform and chloroform react with aldehydes to give iodo- and chloroalkenes **60**, respectively (Eq. 72). (8) When a combination of bromoform and chromium(II) chloride is used, a partial halogen exchange of bromoform with chloride anion occurs before the reaction with the aldehyde to afford a mixture of bromo- and chloroalkenes. This exchange is avoided by using a combination of chromium(III) bromide and lithium aluminum hydride instead of chromium(II) chloride (Eq. 72). (8) The rates of the reaction of the haloform decrease in the sequence  $\text{I} > \text{Br} > \text{Cl}$ . Heating a mixture of chloroform and chromium(II) chloride in tetrahydrofuran to reflux before adding the aldehyde reportedly accelerates the reaction. (172)

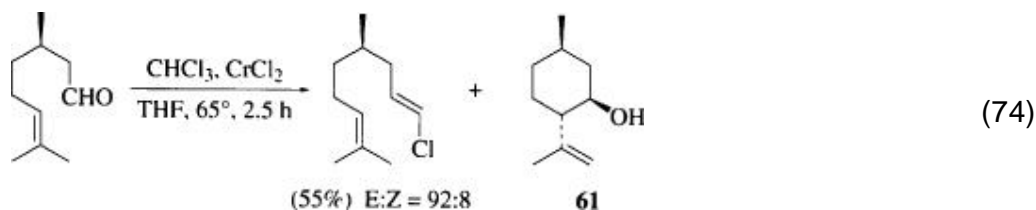


Chromium(II)	X	X'	Conditions	E:Z
CrCl <sub>2</sub>	I	I	0°, 2 h	(82%) 83:17
CrCl <sub>2</sub>	Br	Br	25°, 2 h	(37%) 89:11
		Cl		(32%) 90:10
CrCl <sub>2</sub>	Cl	Cl	65°, 4 h	(76%) 94:6
CrBr <sub>3</sub> , LiAlH <sub>4</sub>	Br	Br	50°, 2 h,	(61%) 87:13

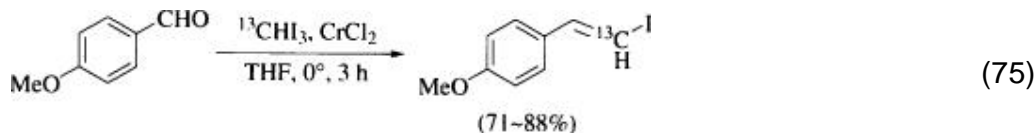
Because the reduction rate of iodoform with zinc is considerably slower than that with chromium(II), use of catalytic amounts of chromium salt in the transformation of aldehydes to iodoalkenes is possible in the presence of zinc, Me<sub>3</sub>SiCl, and NaI in dioxane (Eq. 73). (173)



Chloroolefination of aldehydes with chloroform and chromium(II) chloride requires heating to promote the reaction, and thus, an ene reaction byproduct **61** is obtained when the aldehyde has a suitably positioned double bond (Eq. 74). (8, 174)



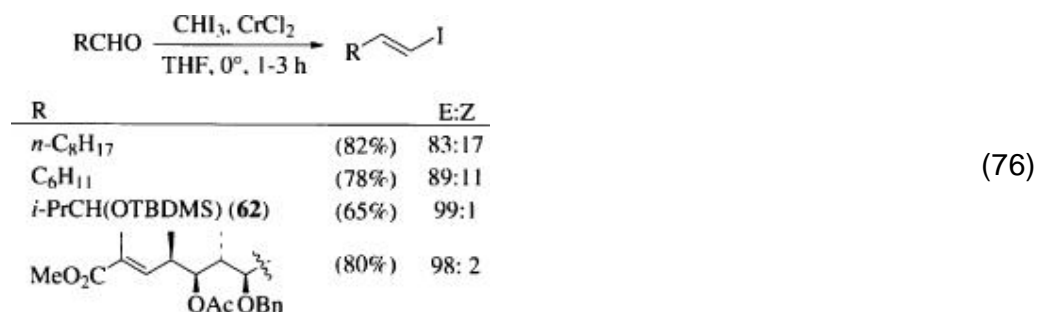
An iodoalkene having a terminal <sup>13</sup>C atom can be prepared by using <sup>13</sup>CHI<sub>3</sub> (Eq. 75). (175)



### 3.4.2. E Selective Formation of Alkenyl Halides

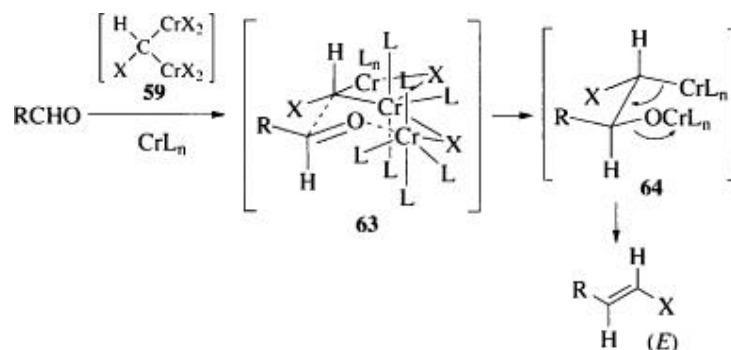
The haloform-chromium(II) chloride reagent produces E alkenyl halides with E:Z ratios of 83:17 to 95:5. The proportion of E alkenyl halides, which depends on the steric size of the aldehyde R substituent, increases in the order I < Br < Cl. As the bulkiness of the substituent R of the aldehyde increases, the E:Z ratio of the alkenyl halides increases (Eq. 76). (8, 176, 177) For example, the E:Z ratios of the iodoalkanes produced from nonanal and

cyclohexanecarboxaldehyde are 83:17 and 89:11, respectively. The reaction of aldehydes having  $\alpha$ -hydroxy groups protected with TBDMS (**62**) and Bn groups affords the corresponding E iodoalkenes almost exclusively. Although the iodoolefination is not very sensitive to the bulkiness near the aldehyde group, the reaction does not proceed with a highly sterically hindered aldehyde. (**178**)



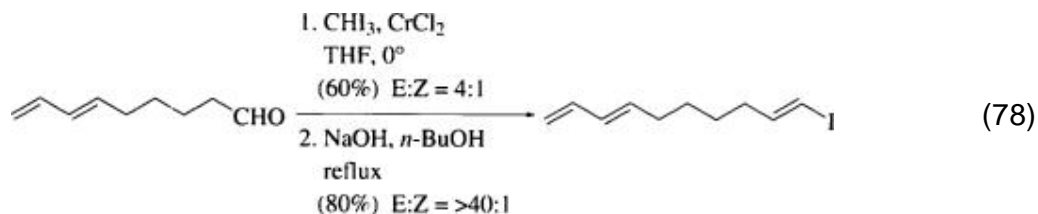
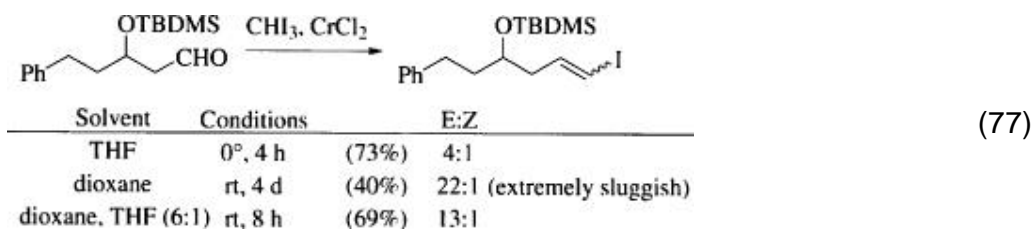
High E selectivity in the formation of haloolefins with the gem-dichromium species is explained by the mechanism summarized in Scheme 11. (**179**, **180**) Addition of the gem-dichromium species **59** to an aldehyde (RCHO) proceeds via a six-membered pseudo-chair transition structure **63** containing two chromium ions bridged by a halogen. Both substituents R and X possess stable equatorial positions in the transition state. Syn elimination of  $(\text{L}_n\text{Cr})_2\text{O}$  from the adduct **64** takes place smoothly, before rotation at the formed single bond, to give an E haloolefin.

Scheme 11.

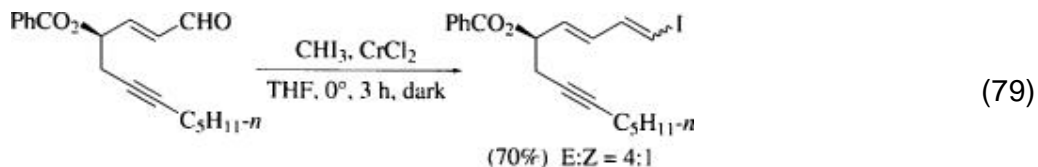


Two methods reportedly improve the E:Z ratio in acyclic systems: 1) Use of a dioxane-tetrahydrofuran solvent mixture (dioxane-THF, 6:1) retards the reaction rate, but considerably improves the E:Z ratio (Eq. **77**); (**181**) 2) Treatment of the iodoalkane mixture with sodium hydroxide in *n*-butanol selectively consumes the minor Z iodoalkene, thereby providing the product with a high E:Z ratio (Eq. **78**). (**182**, **183**)



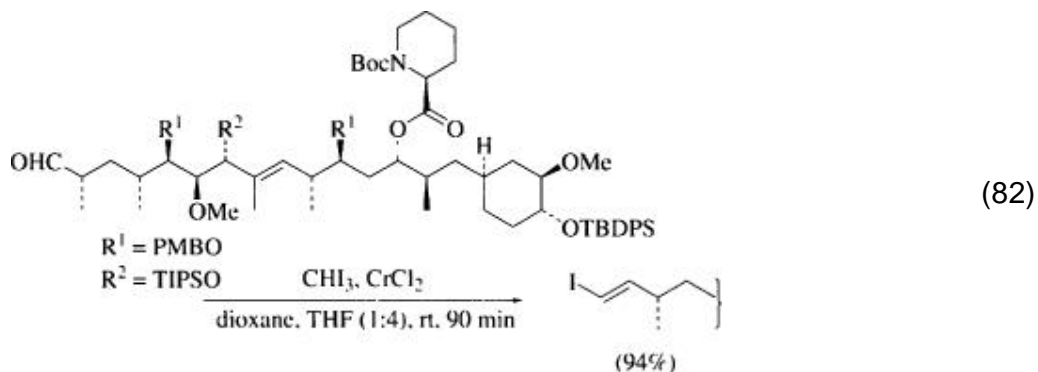
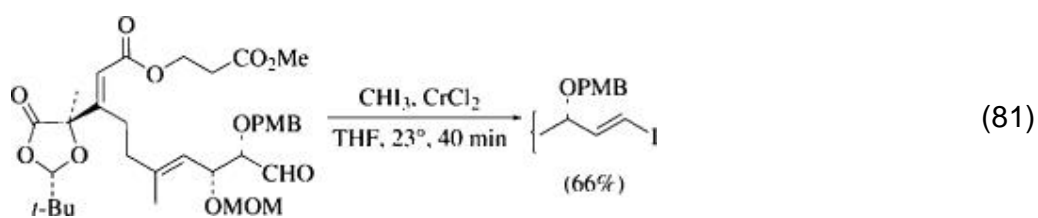
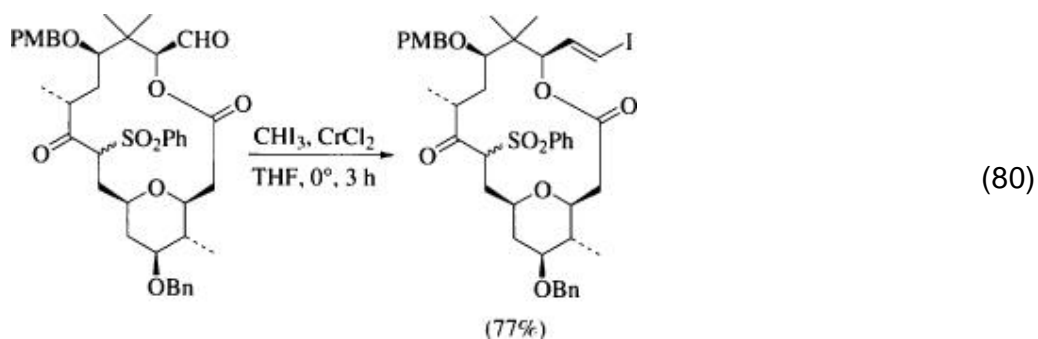


In the case of  $\alpha$ ,  $\beta$ -unsaturated aldehydes, isomerization of the conjugated iododienes sometimes occurs by exposure to acid and light, producing a large proportion (E:Z = ca. 40:60) of the thermodynamically more stable Z isomers (Eq. 79). In such cases, the reactions must be protected from light. (184, 185)



#### 3.4.2.1. Functional Group Selectivity

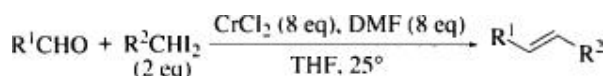
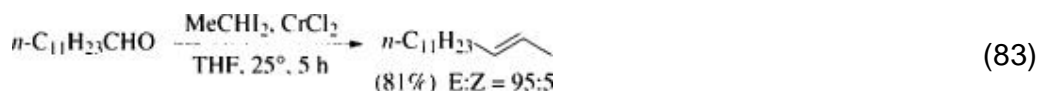
Alkenyl halides can be formed from ketones. However, this transformation requires a longer reaction time and the yield usually drops to about 50% when acyclic ketones are involved. Since ketones are less reactive than aldehydes, an aldehyde can be selectively converted into an E iodoolefin in the presence of a ketone carbonyl (Eq. 80). (8, 186-188) The following functional groups are also tolerated during the reaction: ester, lactone, amide, nitrile, 1,3-diene, acetylene, olefin, alkyl bromide, alkyl chloride and ethylene glycol acetal. Hydroxy groups can be protected as the following groups: -OMe, -OBn, -OTES, -OTIPS, -OTBDMS, -OTBDPS, -OAc, -OCOPh, -OMOM, -OTHP and -OPMB (Eqs. 81 and 82). (189-192) The iodoenolization proceeds in some cases in the presence of an unprotected hydroxy group. (193) Because the geminal dichromium reagent is not highly basic, epimerization at the  $\alpha$  position of the aldehyde does not normally occur.



#### 3.4.2.2. *E* Selective Olefination of Aldehydes

Chromium(II) chloride smoothly reduces 1,1-diiodoethane in tetrahydrofuran to give a 1,1-dichromioethane reagent, which reacts with aldehydes to furnish ethylidenation products in high yield (Eq. 83). (7) Reduction of other gem-diiodoalkanes with chromium(II) chloride proceeds rather slowly, and the desired olefins are obtained in only 10–50% yields. However, activation of chromium(II) chloride with 1 equivalent of dimethylformamide permits a range of gem-diiodoalkanes to be used (Eq. 84). (7) This effect is attributed to the enhanced reducing ability of chromium(II) by coordination to donor ligands. The reactivity of 1,1-dihaloalkanes toward chromium(II) chloride decreases in the order  $\text{I} > \text{Br} > \text{Cl}$ . For example, reaction of 4-isopropylbenzaldehyde with

1,1-diiodo-, 1,1-dibromo- and 1,1-dichloroethane at 25° for 10–24 hours affords 97, 14, and 0% yields of the ethyldienation product, respectively. (7) When diiodomethane is used as the diiodoalkene, methylenation of aldehydes proceeds smoothly in the presence of chromium(II) chloride (or chromium(II) chloride treated with dimethylformamide). (7, 194)



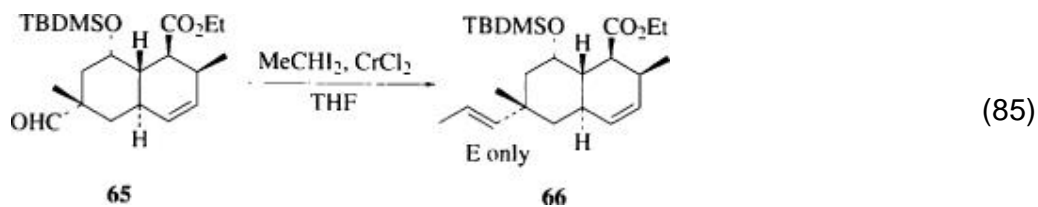
R <sup>1</sup>	R <sup>2</sup>	Time	Yield (%)	E:Z
<i>n</i> -C <sub>8</sub> H <sub>17</sub>	<i>n</i> -Pr	1.5 h	(85%)	96:4
<i>t</i> -Bu	<i>n</i> -Pr	1 h	(96%)	99:1
<i>n</i> -C <sub>5</sub> H <sub>11</sub>	<i>i</i> -Pr	1 h	(74%) <sup>a</sup>	93:7
Ph	<i>i</i> -Pr	2 h	(79%) <sup>a</sup>	88:12
<i>n</i> -Pr	<i>t</i> -Bu	0.5 h	(90%)	94:6
Ph	<i>t</i> -Bu	2 h	(80%)	96:4

<sup>a</sup> R<sup>2</sup>CHI<sub>2</sub> (4 eq), CrCl<sub>2</sub> (16 eq), DMF (16 eq)

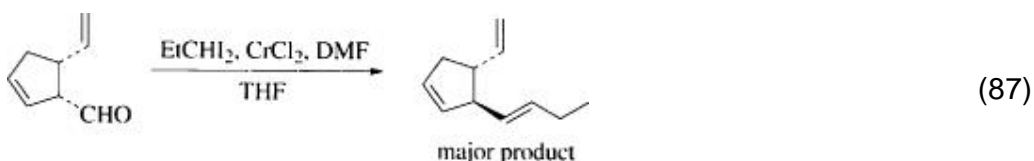
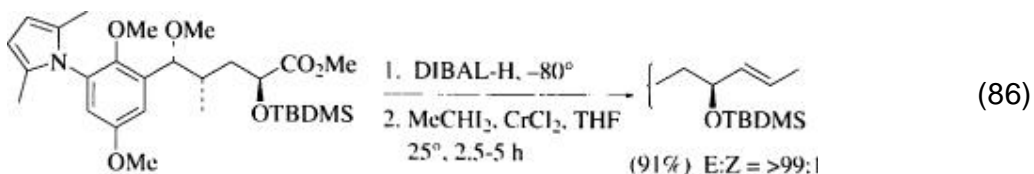
(84)

The 1,1-diiodoalkane-chromium(II) chloride-DMF method provides alkylidenation products with a high level of E selectivity, especially when applied to aliphatic aldehydes. The E:Z ratios increase as the bulkiness of the substituent on the aldehyde (R<sup>1</sup>) is enhanced. This is in contrast to the Wittig reaction, which under saltfree conditions provides Z alkenes with high selectivity. (195, 196)

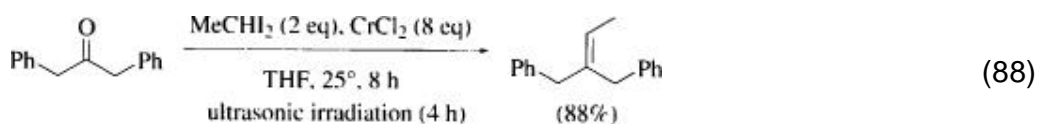
It is difficult to obtain E alkylidenation products from pivalaldehyde by a Wittig reaction even by using Schlosser's β-oxido ylide method. (197) The chromiummediated olefination proceeds smoothly with the sterically congested aldehyde 65, and the E olefin 66 is produced almost exclusively (Eq. 85). (198)



Because the olefination proceeds under mild conditions, functional groups indicated in the haloform-chromium(II) chloride section are also tolerated here. Epimerization at the  $\alpha$  position of aldehydes does not normally take place (Eq. 86), (199, 200) except in cases where the aldehyde is highly prone to enolization (Eq. 87). (201)



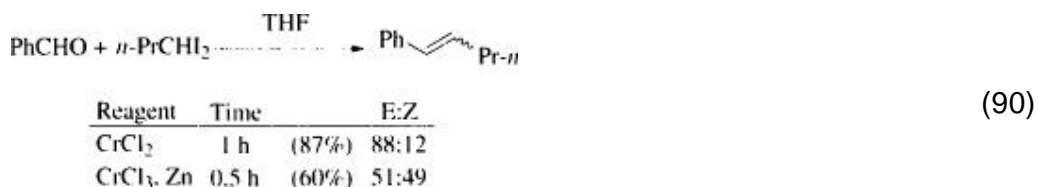
The ethylenation of ketones with 1,1-diiodoethane and chromium(II) chloride proceeds in good yield, even with easily enolizable ketones (Eq. 88). (7) However, yields of the olefination products of ketones with other 1,1-dichromium reagents are rather low. For example, the reaction between benzaldehyde and 2,2-diiodopentane with chromium(II) chloride-dimethylformamide in tetrahydrofuran at 25° gives a complex mixture containing only 7% of the desired trisubstituted olefin (E:Z = 63:37).



When protected hydroxy groups, such as acetoxy or acetal groups, are present next to the diiodo group,  $\beta$ -elimination proceeds smoothly upon treatment with chromium(II) and DMF to give a mixture of E and Z 1-iodoalkenes (Eq. 89). (202)



Olefins are obtained from aldehydes by using chromium(III) chloride and zinc, but the E:Z olefin ratios are lower than those obtained with the chromium(II) chloride (Eq. 90). (7, 203) In contrast to the chromium(II)-mediated reaction, 1-iodobutane is observed by GLPC analysis during the reaction involving zinc. These results suggest that the mechanism of the olefination with chromium(III) and zinc is different from that for the reactions of geminal dimetallic species and aldehydes.

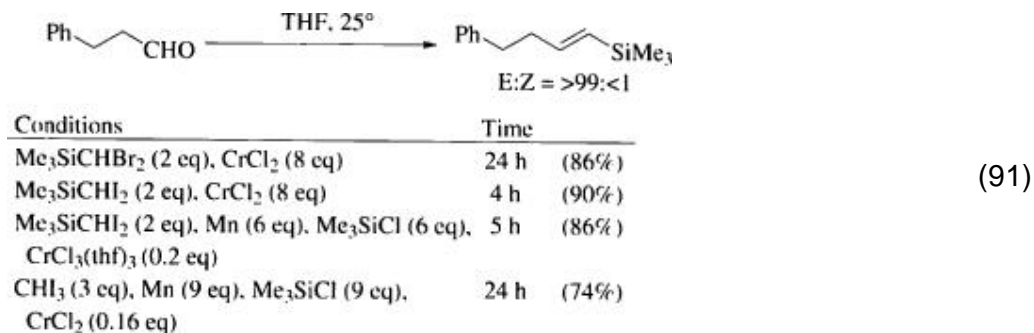


#### 3.4.2.3. E Heterosubstituted Olefins

The chromium-olefination method is applicable to the formation of heterosubstituted olefins, such as alkenylsilanes, (204) alkenyl sulfides, (204) alkenylstannanes, (179, 205, 206) and alkenylboronic esters (180) with high E selectivity. Because olefination reactions using heteroatom-substituted phosphorus ylides are not always highly stereoselective, these heteroolefins are usually prepared from aldehydes by the following sequence: 1) one-carbon homologation of aldehydes to terminal acetylenes (RCHO → RCH = CHBr → RC = CH) and 2) the stereoselective conversion of the terminal acetylenes into the heterosubstituted olefins. The one-step chromium-mediated reactions on the other hand proceed under mild conditions. Thus, an aldehyde can be selectively transformed into heterosubstituted E olefins without affecting coexisting ketone, cyano, ether, acetal, and ester groups.

E Alkenylsilanes are produced stereoselectively from aldehydes with (dibromomethyl)trimethylsilane (207) and chromium(II) chloride (Eq. 91). (204, 208) E Alkenylsilanes are produced exclusively owing to the steric demand of the trimethylsilyl group. This group also facilitates the reduction of geminal dihalogen compounds with chromium(II) chloride, and thus (dibromomethyl)trimethylsilane can be used instead of the corresponding diiodo compound although a long reaction time is required. The amount of chromium salt can be reduced to a catalytic quantity using manganese as a reductant. The easily handled and less hygroscopic chromium(III) salt, CrCl<sub>3</sub>(thf)<sub>3</sub>, can be used for the transformation. Because iodoform is reduced with manganese in the presence of chlorotrimethylsilane to give

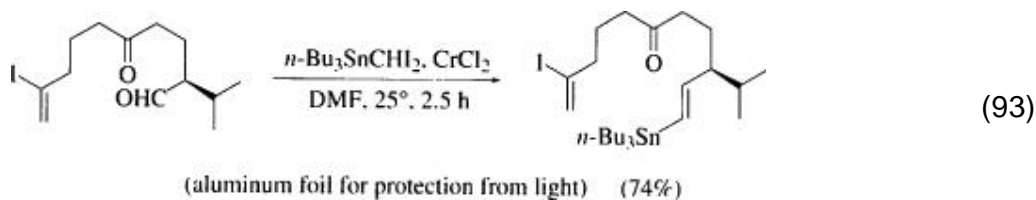
(diiodomethyl)trimethylsilane, a one-pot transformation of aldehydes to E alkenylsilanes is achieved by treatment with iodoform, manganese, chlorotrimethylsilane, and a catalytic amount of chromium(II) chloride in THF. (209)



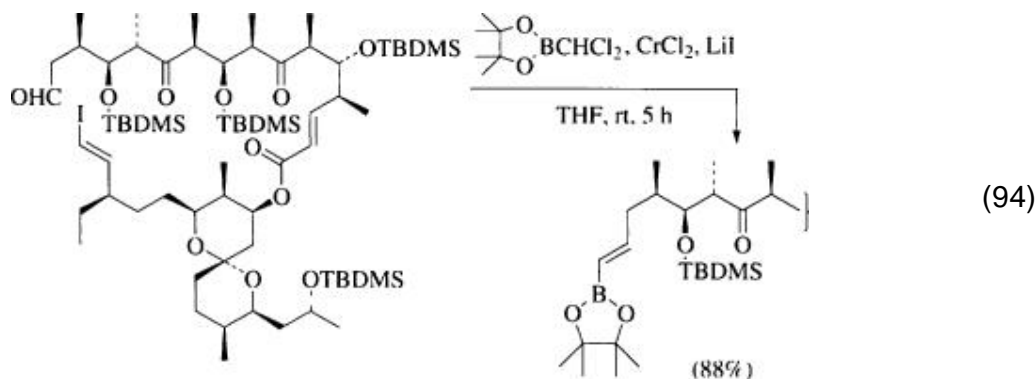
Ultrasonic irradiation of the mixture at 55 to 60° accelerates the reaction and sometimes minimizes epimerization at the α position of the aldehyde (Eq. 92). (210)



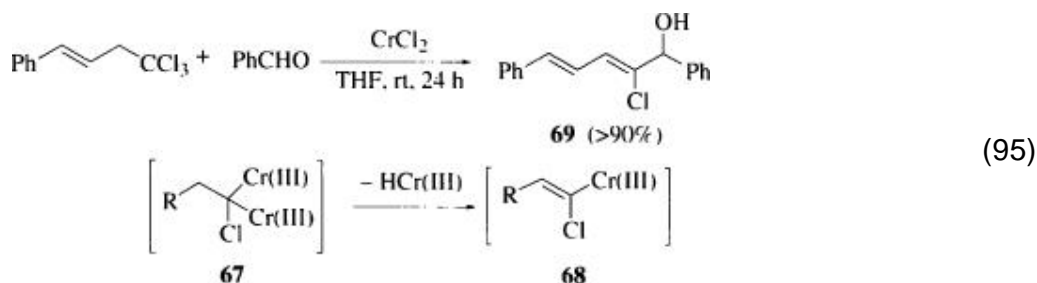
The conversion of aldehydes into alkenylstannanes with one-carbon homologation proceeds when (dibromomethyl)- or (diiodomethyl)tributylstannane is used instead of (dibromomethyl)trimethylsilane. (179, 205, 211) As (dibromomethyl)tributylstannane is not easy to reduce with chromium(II) chloride in tetrahydrofuran, chromium(II) chloride must first be treated with 1 equivalent of dimethylformamide and lithium iodide. In contrast, a geminal dichromium reagent is smoothly generated using (diiodomethyl)tributylstannane in dimethylformamide. The transformation is useful for the preparation of alkenylstannanes having ketone, ester, cyano, or acetal groups (Eq. 93). (212)



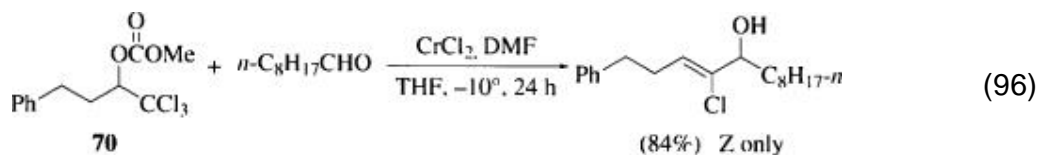
E Alkenylboronic esters are prepared from aldehydes with high stereocontrol using dibromomethylboronic ester (213, 214) and chromium(II) chloride in THF. (180) Lithium iodide is essential to promote the reaction. The role of lithium iodide may be to form diiodomethylboronic ester in situ, which would be more prone to undergo reduction with chromium(II) chloride. The bulkiness of the pinacol group is important for the high E-selectivity. For example, the reaction of hexanal with  $(RO)_2BCHCl_2[(RO)_2 = OCH_2CMe_2CH_2O]$  gives a 3:1 mixture of the E and Z alkenylboronic esters under the same reaction conditions. (215) Ketone, ester, and acetal groups are tolerated during the transformation (Eq. 94). (216) The synthesis of E alkenylboronic esters can also be accomplished using a catalytic amount of a chromium salt, manganese, and  $Me_3SiCl$ . (217)



The rate of  $\beta$ -elimination from geminal dichromium compounds is not as fast as the rate of addition of the geminal dichromium compounds to aldehydes. However, dichromium compounds 67 with a geminal chlorine atom undergo the  $\beta$ -elimination smoothly to give a Z  $\alpha$ -chloro-substituted alkenylchromium compound 68, which adds to an aldehyde to afford Z 2-chloro-2-alken-1-ol 69 stereoselectively (Eq. 95). (79)



A similar coupling reaction proceeds by treatment of a mixture of an aldehyde and a carbonate ester of 2,2,2-trichloroethanol derivative **70** with chromium(II) chloride–DMF in THF (Eq. 96). (53)

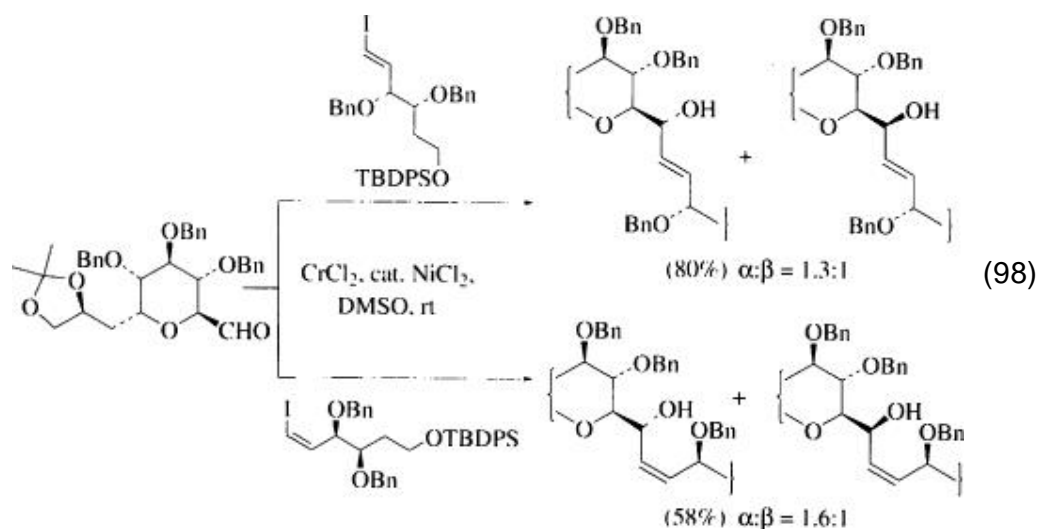
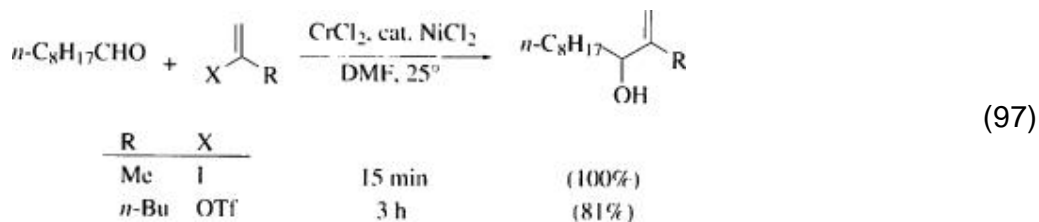


### 3.5. Alkenylchromium Reagents

#### 3.5.1.1. Preparation under Nickel Catalysis

Chromium(II) chloride reduction of alkenyl and aryl iodides (or bromides) to alkenyl- and arylchromium reagents and subsequent Grignard-type carbonyl addition was first performed without a catalyst. (9) The results were not consistent with the observation that alkenyl and aryl halides are difficult to reduce with chromium(II). (1) Later, it was found that the success of the reaction depends on the source and batch of chromium(II) chloride, and that a trace amount of nickel(II), a major contaminant of the effective commercial chromium(II) salt, is a key catalyst for the coupling. (10, 11) A catalytic amount of nickel is indispensable to promote the Grignard-type carbonyl addition of halo alkenes to aldehydes with good reproducibility (Eqs. 97 and 98). (9-11) Normally 0.1-1 wt% of nickel(II) chloride is added to chromium(II) chloride. Nickel acetylacetonate (218, 219) and Ni(cod) (220) are reportedly effective in some reactions. It is important to keep the content of nickel(II) chloride low (about 0.01-1 wt%) to avoid the formation of dienes by homocoupling of the halo alkenes. (221) Other potential catalysts, such as manganese(II) chloride iron(III) chloride, cobalt(II) chloride, copper(I) chloride, and palladium(II) chloride are not as effective.



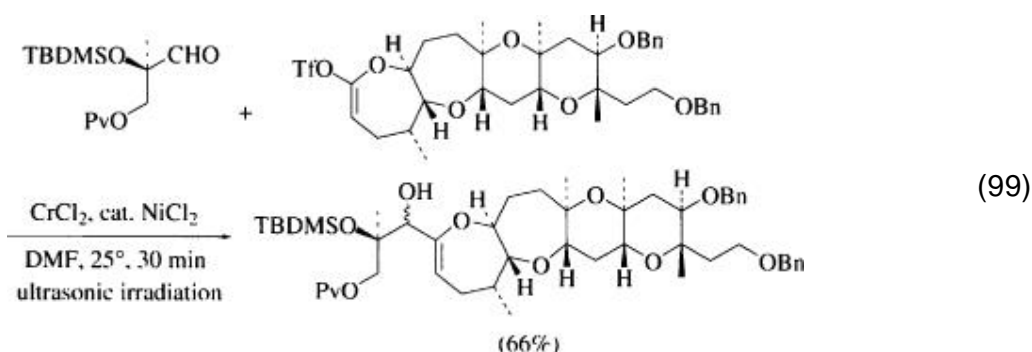


A soluble form of chromium(II) chloride is essential to promote a smooth reaction. Dimethylformamide, dimethyl sulfoxide, dimethyl sulfoxide-dimethyl sulfide, and a mixture of dimethylformamide and tetrahydrofuran are the preferred solvents, and should be dried and deoxygenated. Little or no reaction occurs in ether or tetrahydrofuran alone. Addition of pyridine ligands, especially 4-*tert*-butylpyridine, to a mixture of chromium(II) chloride and nickel(II) chloride in THF gives a homogeneous solution. (222) The additive accelerates the reactions of alkenyl halides (or triflates) with aldehydes, (222, 223) and also inhibits homo-coupling of the alkenyl halides (or triflates), even when the amount of nickel is increased to 0.5 mol relative to the chromium(II) chloride. When 2 equivalents of lithium chloride are added to a suspension of chromium(II) chloride in tetrahydrofuran, the chromium salt dissolves. This  $\text{CrCl}_2 \cdot 2\text{LiCl}$  solution can also be used for the nickel-catalyzed coupling reaction. Ultrasonic irradiation is reported to accelerate the reaction sometimes.

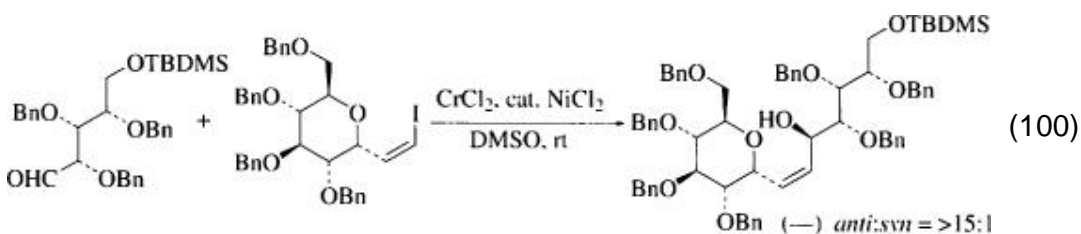
Reaction workup is typically accomplished by addition of the reaction mixture to water and extraction with ether (or ethyl acetate). When separation of the organic and aqueous phases is difficult, addition of sodium (or potassium) serinate, (222) potassium sodium tartarate tetrahydrate (Rochelle salt),

ethylenediamine, (222) or sodium (or potassium) fluoride to the reaction mixture sometimes improves the efficiency of extractive workup.

Iodoalkenes are more reactive than bromoalkenes, and product yields are generally better with the former. The Grignard-type reaction between alkenyl triflates (or mesylates) and aldehydes also proceeds under the same conditions (Eq. 99). (10, 224)

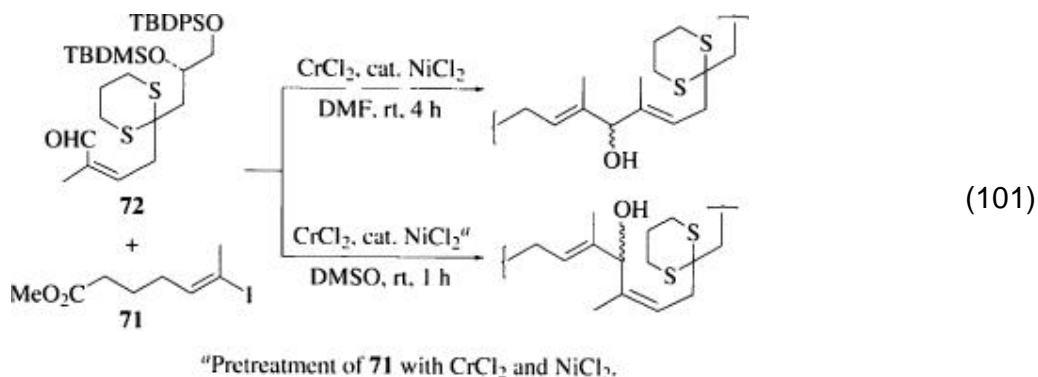


In contrast to traditional reactions with alkenyllithium, -magnesium, and -cuprate reagents, the alkenylchromium reaction is experimentally simple. The reaction can be accomplished by adding a mixture of an aldehyde and a haloalkene to a stirred mixture of chromium(II) chloride and a catalytic amount of nickel(II) chloride in dimethylformamide or dimethyl sulfoxide (or vice versa). Conventional organolithium or -magnesium reagents are sometimes difficult to generate from highly-oxygenated, multifunctional substrates, and the chromium protocol offers a solution to anionic coupling at the alkenyl positions of such substrates (Eq. 100). (11, 225-228)



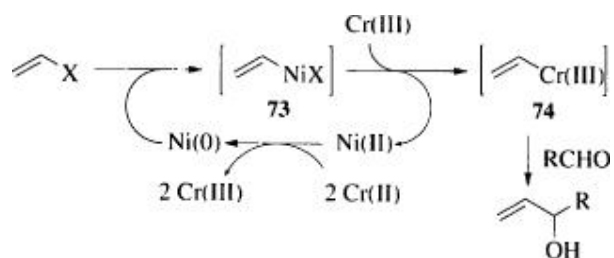
Alkenylchromium reagents produce 1,2-addition products from reactions with  $\alpha$ ,  $\beta$ -unsaturated aldehydes. The configuration of the  $\alpha$ ,  $\beta$ -unsaturated aldehydes is usually maintained, although isomerization of double bonds occurs in some cases. The isomerization can be prevented by changing the solvent from DMF to DMSO and pretreating the alkenyl iodide 71 with

chromium(II) chloride and a catalytic amount of nickel(II) chloride before addition of the  $\alpha$ ,  $\beta$ -unsaturated aldehyde **72** (Eq. 101). (229)

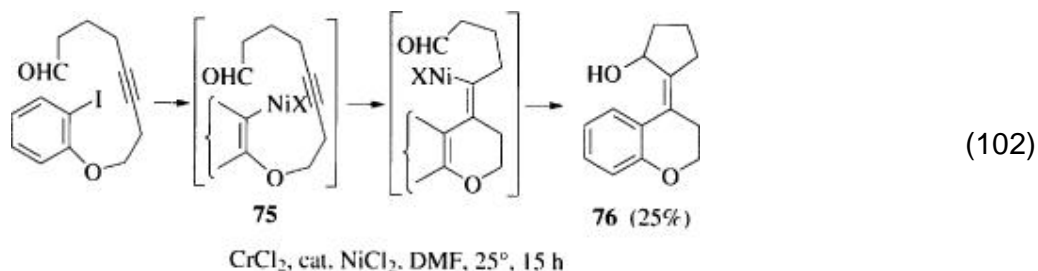


The nickel-catalyzed Grignard-type addition of alkenylchromium reagents to aldehydes is likely to proceed according to the mechanism of Scheme 12. (10) Nickel(II) chloride is first reduced to nickel(0) with 2 equivalents of chromium(II) chloride. Oxidative addition of an alkenyl halide to the nickel(0) occurs, then the transmetalation reaction between the resulting alkenylnickel species **73** and the chromium(III) salt affords an alkenylchromium reagent **74**, which reacts with an aldehyde to produce the allylic alcohol.

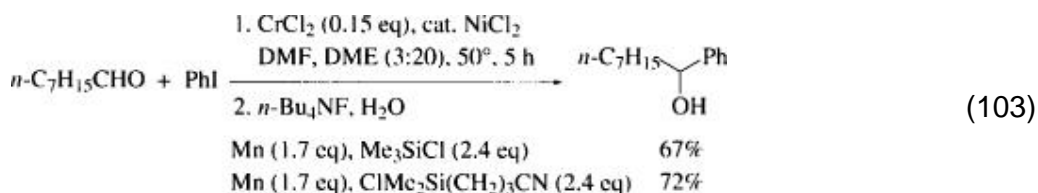
Scheme 12.



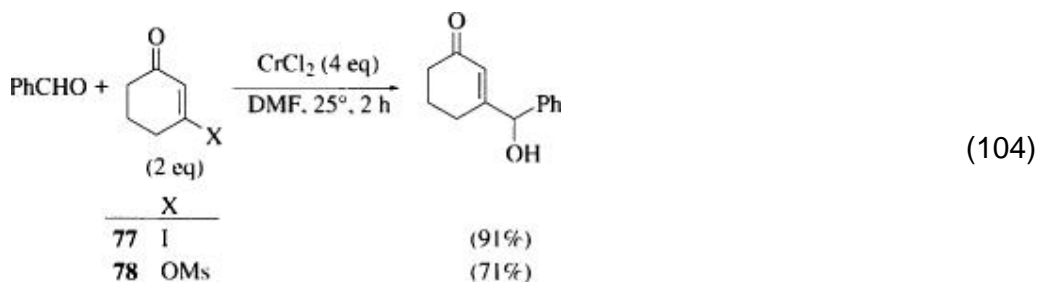
The addition of aryl halides to aldehydes is likely to proceed by the same mechanism. The intermediate arylnickel species **75** can be intercepted by an internal carbon-carbon triple bond before the reaction with a formyl group (Eq. 102). (230) The product **76** of syn addition across the triple bond is obtained selectively.



Because manganese metal does not reduce alkenyl halides directly, the amount of the chromium(II) salt can be reduced to a catalytic quantity using manganese as a reductant (Eq. 103). (15, 44) Addition of a chlorosilane is necessary to generate a reducible chromium(III) halide. The yield indicated refers to the product obtained after desilylation.



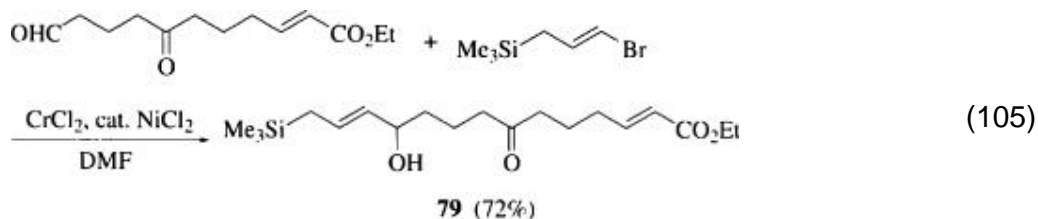
When an electron-withdrawing group, i.e., ketone, ester, or sulfonate group, is attached to the  $\beta$ -position of a halo alkene, the coupling reaction proceeds without addition of a nickel salt (Eq. 104), (63) but the yields are generally lower. Instead of a  $\beta$ -iodo- $\alpha, \beta$ -unsaturated ketone **77**, a vinylic mesylate **78** can be used.



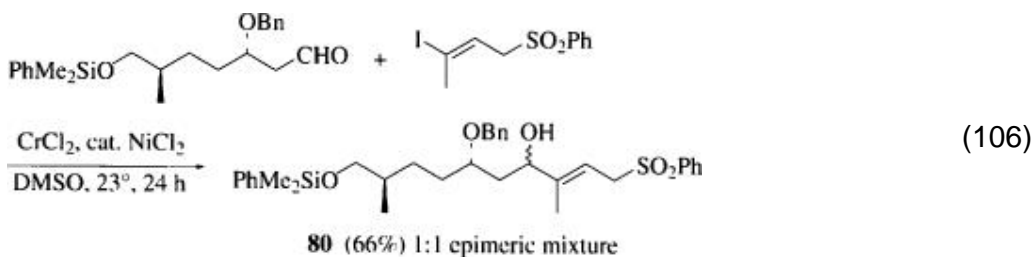
### 3.5.1.2. Functional Group Selectivity

Alkenylchromium reagents add to ketones in ca. 40% yield owing to the low nucleophilicity of the reagents. Aldehyde-selective additions can be accomplished in good to excellent yields without affecting coexisting ketone,

ester, amide, acetal, nitrile, and sulfinyl groups (Eq. 105). (231) The Lewis acidity of chromium(III) in dimethylformamide is moderate and the allylsilane moiety in **79** survives the reaction.

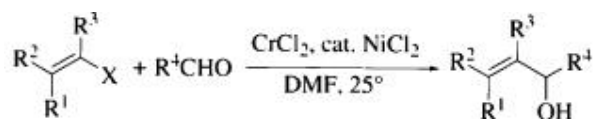


The alkenylchromium reagent is not very basic; epimerization at the  $\alpha$ -position of the aldehyde does not normally occur. The regiochemistry of the double bond is not isomerized during the coupling reaction even when the compound (such as **80**) has a highly acidic allylic proton (Eq. 106). (232)



### 3.5.1.3. Double Bond Stereoselectivity

The configuration of trans and cis disubstituted halo alkenes and trisubstituted trans-halo alkenes is retained in the reaction (Eqs. 98 and 100). (10, 11) Reactions of (*E*)- and (*Z*)-2-bromostyrene and benzaldehyde proceed stereospecifically (Eq. 106a, entries 1 and 2). Treatment of a trisubstituted cis halo alkene (or an alkenyl triflate) with the chromium(II)-nickel(II) system often results in a cis-trans isomerization-coupling reaction sequence, or occasionally in the recovery of the starting alkenyl halide because of steric interactions of substituents cis to the halogen. For example, both (*E*)- and (*Z*)-2-iodo-1-phenyl-1-propene react with benzaldehyde to give (*E*)-1,3-diphenyl-2-methyl-2-propen-1-ol as the sole product (Eq. 106a, entries 3 and 4). (9, 10) Similar isomerization also occurs in the reaction of the highly oxygenated aldehyde **81** with the trisubstituted cis iodo alkene **82** (Eq. 107) (11) and in the reaction using a trimethylsilyl-substituted cis bromo alkene. (233)

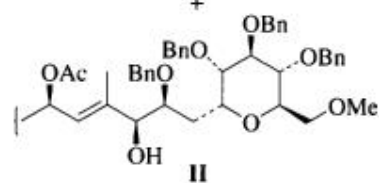
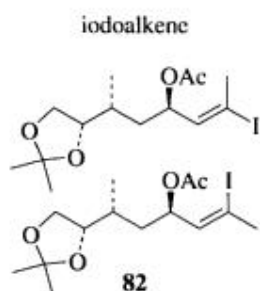
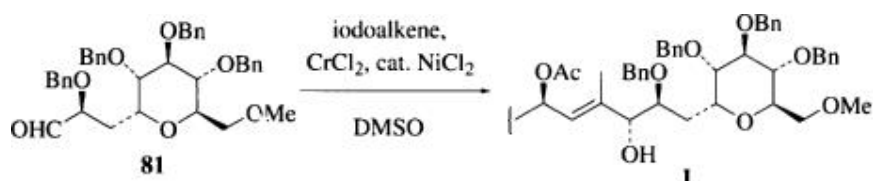


Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	X	Time	
1	H	Ph	H	Ph	Br	1 h	(82%)
2	Ph	H	H	Ph	Br	1 h	(78%)
3	H	Ph	Me	Ph	I	3 h	(91%)
4	Ph	H	Me	Ph	I	3 h	(90%) <sup>a</sup>
5	H	-(CH <sub>2</sub> ) <sub>4</sub> -	Ph	Ph	OTf	1 h	(74%)
6	Me	-(CH <sub>2</sub> ) <sub>4</sub> -	<i>n</i> -C <sub>8</sub> H <sub>17</sub>	Ph	OTf	1 h	(0%) <sup>b</sup>

(106a)

<sup>a</sup>The same allylic alcohol as in entry 3 is produced because of isomerization occurring before addition to benzaldehyde.

<sup>b</sup>The reactant triflate was recovered in 79% yield after being heated at 60° for 6 h.



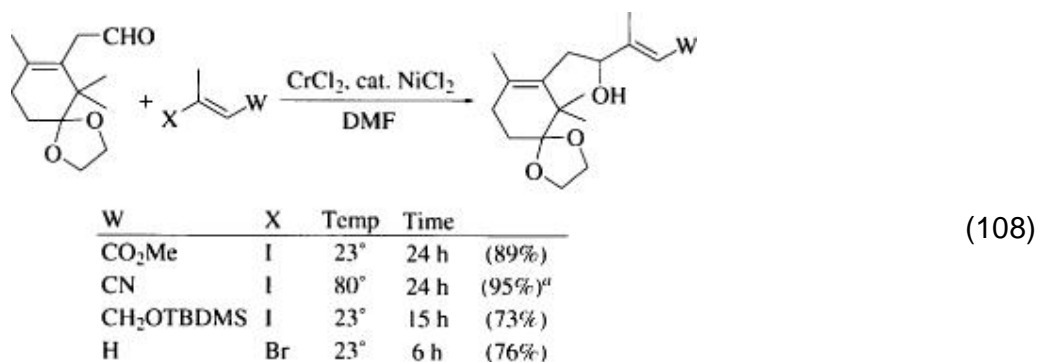
(86%) I:II = 2:1

(15%) I:II = 2:1<sup>a</sup>

<sup>a</sup>Isomerization of the double bond has occurred.

(107)

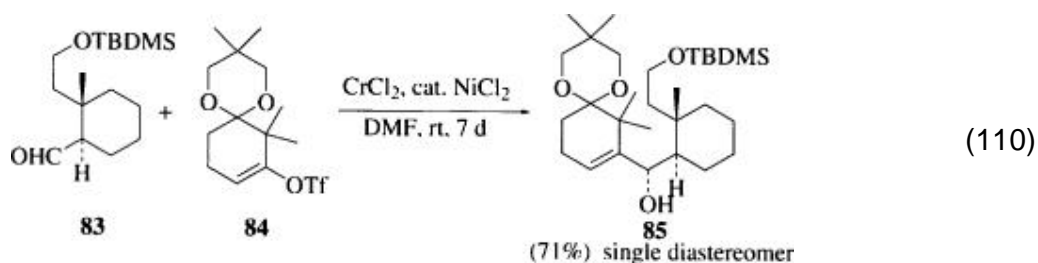
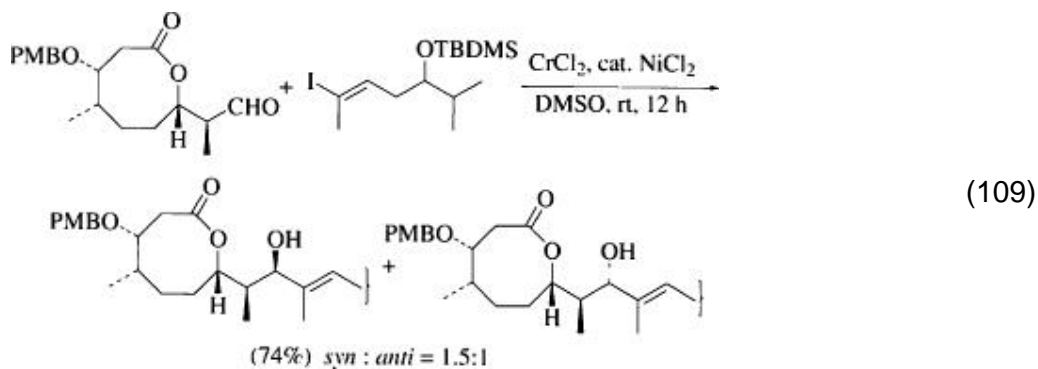
Iodo alkenes with electron-withdrawing groups, such as β -iodo esters, (228, 234) ketones, (11) and nitriles, (234) react cleanly with aldehydes to afford the corresponding E allylic alcohols. The rate of this reaction is much slower than that of 2-iodopropene and even 2-bromopropene with the same aldehyde (Eq. 108). (234)



<sup>a</sup>Addition of more iodocrotononitrile was necessary to complete the reaction.

#### 3.5.1.4. Diastereoselectivity of Reactions with Chiral Aldehydes

The reaction of chiral aldehydes with alkenylchromium reagents produces a mixture of two diastereomers with a moderate to good selectivity for the Felkin isomer. Syn adducts predominate from  $\alpha$ -methyl-substituted secondary aldehydes, but the diastereoselectivity is typically less than 2:1 (Eq. 109). (235) A reaction between the sterically congested aldehyde **83** and the hindered alkenyl triflate **84** produces a single diastereomer **85**, probably because of the steric demands of the two substrates (Eq. 110). (236)

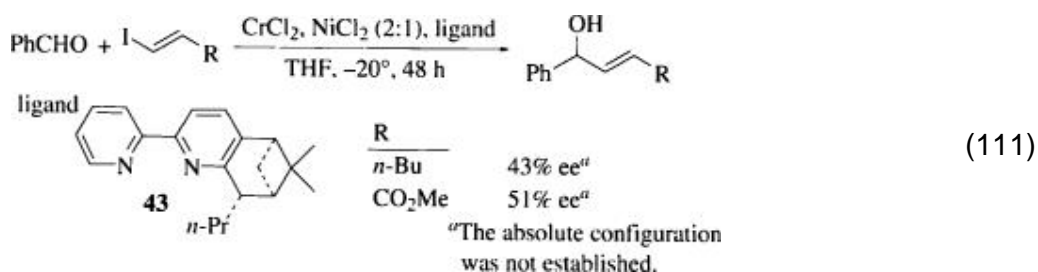


Reactions between  $\alpha$ -alkoxy aldehydes and alkenylchromium reagents normally produce anti adducts as the main products (Eqs. 98, 100, and 116). (11, 237, 238) The diastereoselectivities are 1.3:1 to 15:1 and vary with the nature of the aldehyde and of the alkenylchromium reagent.

The influence of aldehyde  $\beta$ -alkoxy substituents upon the product diastereoselectivity is not great (Eq. 106), (239) but high selectivity is occasionally realized. (228)

### 3.5.1.5. Enantioselective Addition with Chiral Ligands

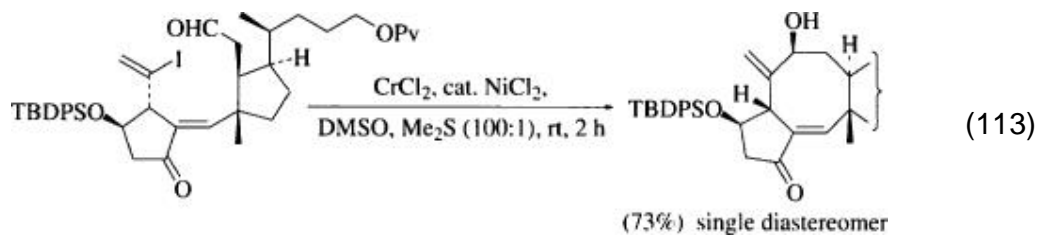
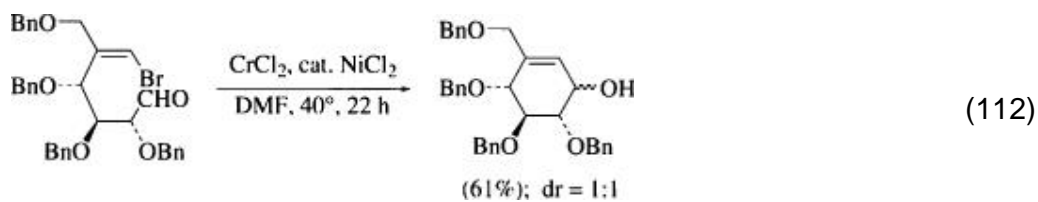
The coupling reaction between an iodoalkene and an aldehyde proceeds smoothly in the presence of 2,2'-dipyridyl ligands such as **43** with a substituent at the 6-position. (133) This observation is in sharp contrast to the reactions with 2,2'-dipyridyl, 1,10-phenanthroline, CHIRAPHOS, or 4,4'-disubstituted bis(oxazoline) as ligands, for which no coupling is observed. In the presence of the 6-substituted 2,2'-dipyridyl **43**, homocoupling of the iodoalkene is suppressed even with a 2:1 mixture of chromium(II) chloride and nickel(II) chloride. Moreover, the coupling reaction with these ligands proceeds smoothly at  $-20^\circ$  in tetrahydrofuran. Moderate asymmetric induction is observed with a simple aldehyde when a stoichiometric amount of the chiral 2,2'-dipyridyl ligand is employed in tetrahydrofuran (Eq. 111). (133) A high level of asymmetric induction ( $dr = 8-10:1$ ) is achieved with a chiral aldehyde having an  $\alpha$ -asymmetric center. (133)



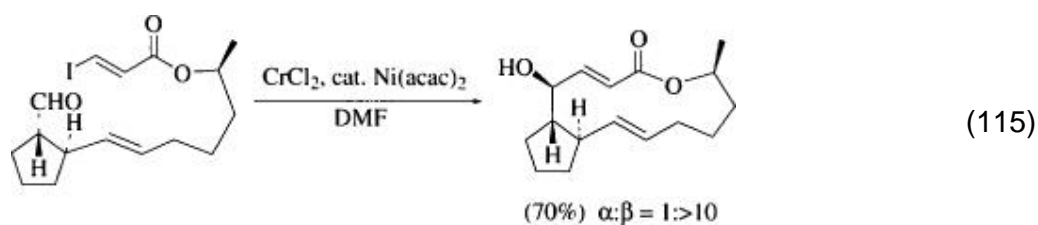
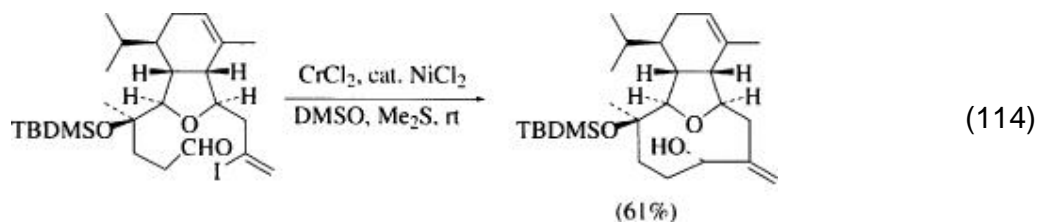
### 3.5.1.6. Intramolecular Cyclization

Because alkenylchromium reagents can be prepared in the presence of aldehydes, the protocol is suitable for intramolecular cyclization. Five-membered, (233, 240, 241) 6-membered (Eq. 112), (242) 7-membered, (243) 8-membered (Eq. 113), (244, 245) 10-membered, (246) 11-membered, (247) and 12-membered carbocycles (248, 219) are effectively constructed by intramolecular cyclization with chromium(II) chloride and nickel catalysts.

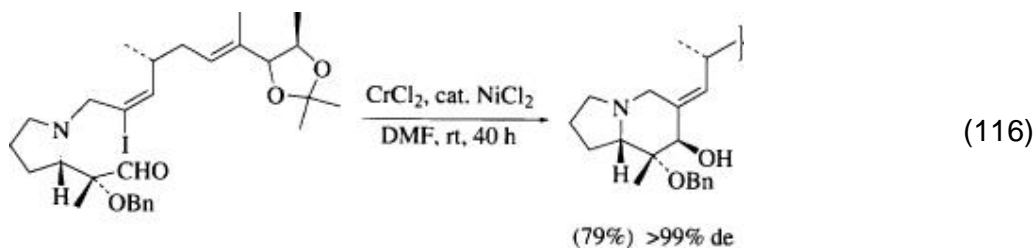




Oxygen-containing 9-membered (Eq. 114), (249, 250) 13-membered (Eq. 115), (218) and 16-membered rings (251) are also formed by using this method.



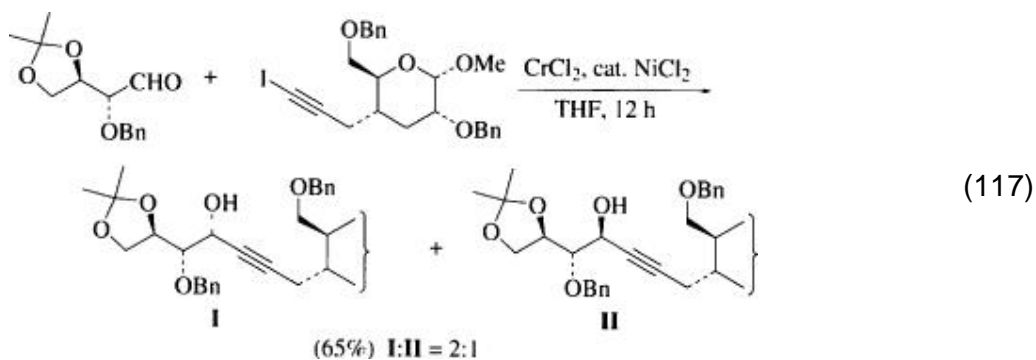
Five-membered (252) and six-membered rings (Eq. 116) (253, 238) containing nitrogen atoms are also constructed with the chromium(II)-nickel(II) system.



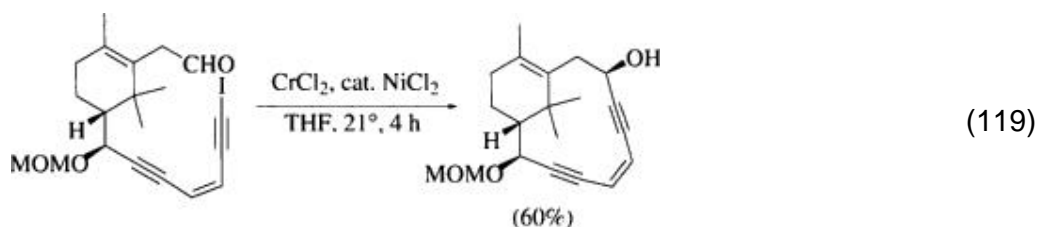
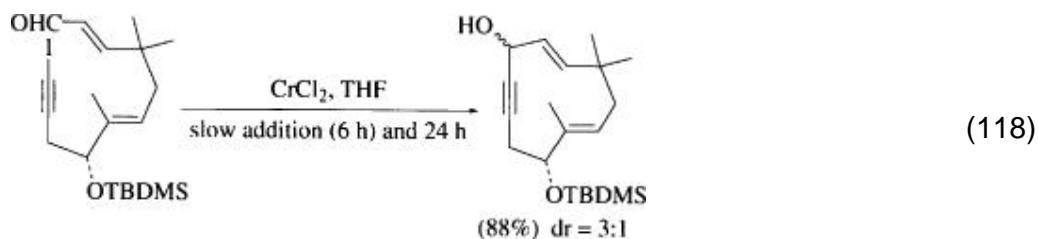
### 3.6. Alkynylchromium Reagents

Although  $\text{CrCl}_2$  mediated reactions between simple halo alkynes and aldehydes proceed without a catalytic amount of nickel(II) chloride, (12) the chromium(II) chloride-nickel(II) chloride system is used for highly oxygenated substrates (254, 255) and for intramolecular cyclizations. (13, 14) The amount of nickel(II) chloride used for iodoalkyne addition to carbonyl groups is smaller (0.01–0.1% w/w) than that for iodoalkenes.

Potential problems, such as epimerization and dehydration associated with enolization do not occur (Eq. 117). (254, 255) The diastereofacial selectivity of the addition of alkynylchromium reagents to aldehydes is moderate, and the diastereomeric ratio varies (8.3:1 to 1:2) with the aldehyde structure. (254-256)



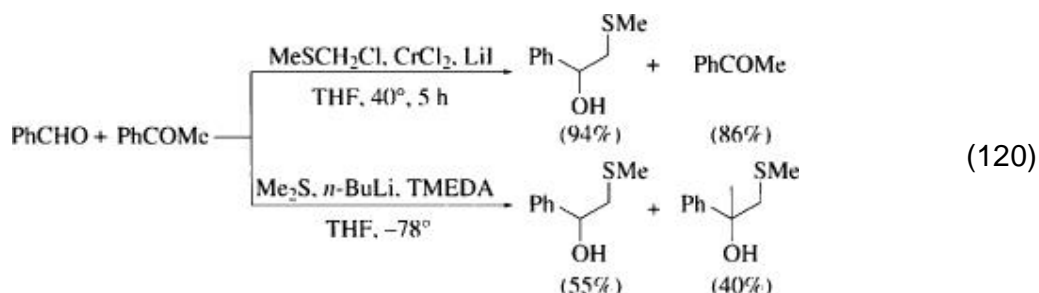
The starting 1-iodo-1-alkynes can be prepared from 1-alkynes with iodine and morpholine in excellent yields under mild conditions. (255) Thus, the reaction is suitable for intramolecular cyclization (Eq. 118). (257-259) Nine-, (260) ten-, (13, 14, 261-265) and twelve-membered rings (266) are prepared by intramolecular cyclization with chromium(II) chloride and a catalytic amount of nickel(II) chloride. Notably, this method has been used to synthesize endiynes (Eq. 119). (266)



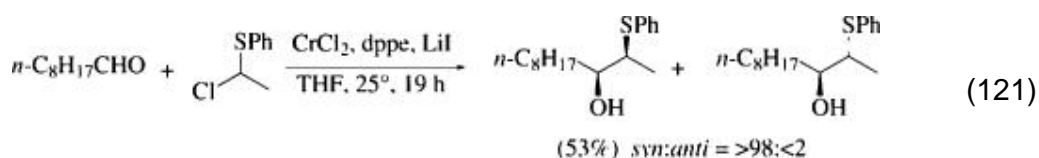
A low concentration of the  $\omega$ -iodoalkynyl aldehyde is occasionally required to prevent intramolecular coupling and/or dehalogenative reduction. (261, 260)

### 3.7. Sulfur- and Nitrogen-Substituted Alkylchromium Reagents

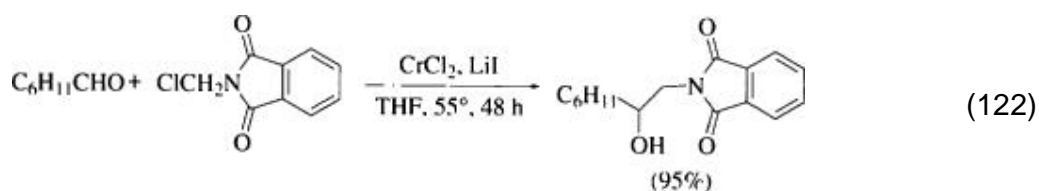
Compared to their sulfinyl and sulfonyl counterparts, the preparation of  $\alpha$ -sulfenyl carbanions by deprotonation requires strong base combinations such as *n*-butyllithium/1,4-diazabicyclo[2.2.2]undecane, (267) *n*-butyllithium/tetramethylethylenediamine, (268) or *tert*-butyllithium/hexamethylphosphoric triamide. (269, 270) In contrast, the reduction of  $\alpha$ -haloalkyl phenyl or methyl sulfides proceeds smoothly with chromium(II) chloride in the presence of lithium iodide to generate the corresponding  $\alpha$ -thioalkylchromium reagents. These agents add to aldehydes in a chemo- and stereoselective manner unattainable under highly basic conditions. For example, exposing a mixture of benzaldehyde and acetophenone at  $-78^\circ$  to methylthiomethyl lithium, prepared by using *n*-butyllithium/tetramethylethylenediamine, gives a mixture of 2-methylthio-1-phenylethanol and 1-methylthio-2-phenyl-2-propanol in a 7:5 ratio (Eq. 120). (271) In contrast, the chromium reagent does not react with acetophenone, which is recovered unchanged in 86% yield. In the reaction of an  $\alpha$ ,  $\beta$ -unsaturated aldehyde, the 1,2-addition product is produced exclusively. (271)



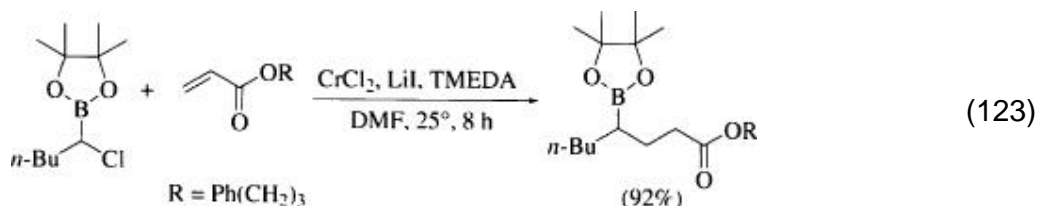
The (1-phenylthio)ethylchromium reagents prepared in this manner add to aldehydes with high stereocontrol in the presence of suitable ligands such as 1,2-diphenylphosphinoethane (dppe) (Eq. 121). (271)



The reduction of *N*-(chloromethyl)succinimide or -phthalimide with  $\text{CrCl}_2$  in the presence of LiI provides the corresponding  $\alpha$ -nitrogen-substituted organochromium reagents, which react in situ with aldehydes to give protected amino alcohols in good yields (Eq. 122). (272) The reaction tolerates the presence of functional groups such as nitrile and ester.



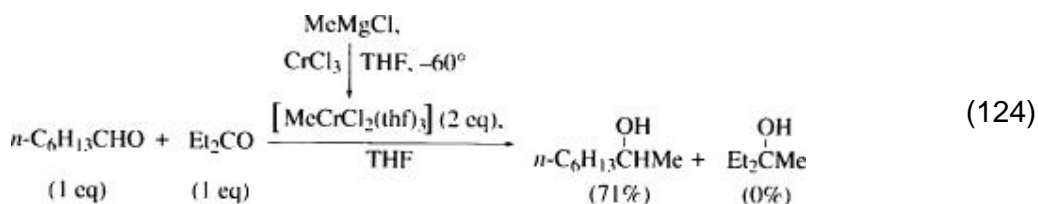
In contrast to sulfur and nitrogen atoms, an  $\alpha$ -boronate substituent does not accelerate the second one-electron reduction leading to the corresponding organochromium compound, and the generated  $\alpha$ -boryl radical adds to an  $\alpha, \beta$ -unsaturated ester in a 1,4 fashion (Eq. 123). (273)



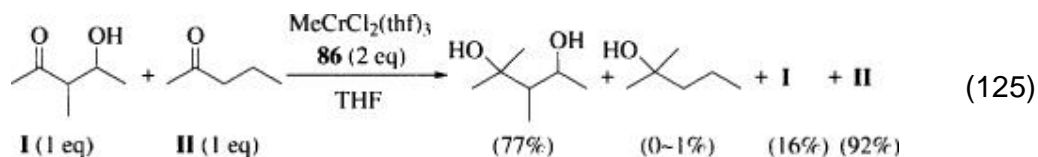
### 3.8. Alkylchromium Reagents

#### 3.8.1.1. Preparation by Transmetalation

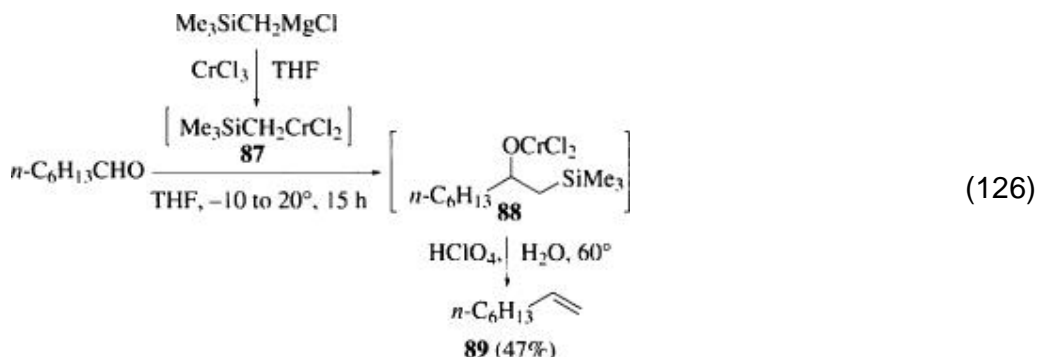
Alkylchromium compounds can be prepared by treating a chromium(III) salt, such as chromium(III) chloride or chromium(III) acetylacetonate, with an organomagnesium, (70) -lithium, or -aluminum compound. (72, 95) The methylchromium(III) compound, prepared in situ from a methyl Grignard reagent and chromium(III) chloride in tetrahydrofuran at 60°, reacts selectively with an aldehyde (Eq. 124). (274)



This alkylation reaction is accelerated by adding 1–3 equivalents of ethanol or water to the reaction mixture. (88) The associated increase in reaction rate suggests that 1–3 equivalents of the protic molecules are incorporated into the ligand sphere of the chromium reagent in place of tetrahydrofuran, and that they act primarily as donor ligands because of the slow rate of protonolysis of the carbon-chromium bond compared with carbon-lithium or -magnesium bonds. This accelerating effect of coordinated donor ligands accounts for the chemoselective addition of monoalkylchromium(III) reagents **86** to ketones with  $\alpha$  - or  $\beta$ -hydroxy, methoxy, or dimethylamino groups (Eq. 125). (71, 109)



When trimethylsilylmethylchromium **87** is used, the aldehyde addition products **88** can be transformed into terminal olefins **89** with acid (Eq. 126). (275)

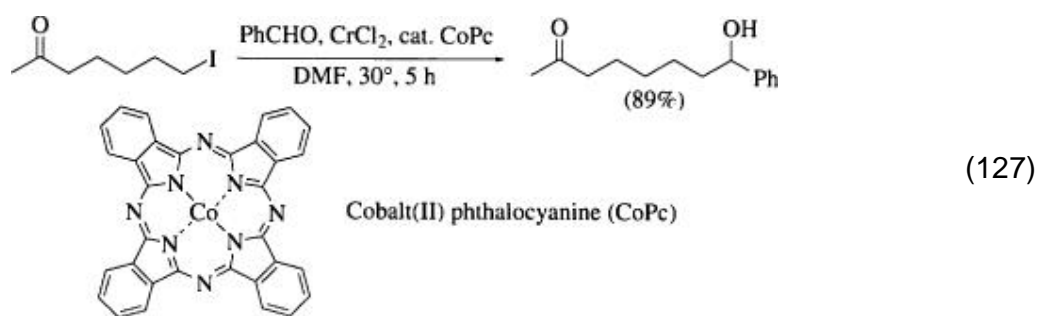


### 3.8.2. Reduction of Alkyl Halides with Chromium(II) Chloride under Cobalt Catalysis (51)

Reactive substrates such as allylic or alkynyl halides are readily reduced by chromium(II) salts. It is difficult, however, to reduce alkyl halides to alkylchromium reagents in aprotic solvents. For example, treatment of a mixture of 1-iodododecane and benzaldehyde with chromium(II) chloride in dimethylformamide at 30° for 16 hours affords only 7% of 1-phenyl-1-tridecanol, and most of the halide is recovered as 1-chlorododecane (88%). This result suggests that the rate of substitution by chloride ion (Eq. 11, step A) is higher than the rate of reduction with chromium(II) ion (Eq. 11, step B). The reduction of the alkyl radical with chromium(II) ion leading to an alkylchromium(III) species (Eq. 11, step C) is rapid. Addition of a catalytic amount of vitamin B<sub>12</sub> (B<sub>12</sub>) or cobalt phthalocyanine (CoPc) accelerates the formation of alkyl radicals from alkyl halides, especially 1-iodoalkanes, (Eq. 11, step B), and the Grignard-type reaction of alkylchromium reagents then proceeds smoothly.

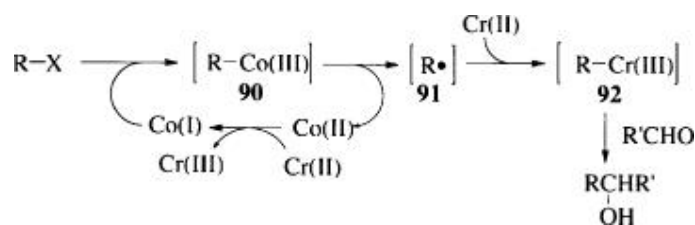
The reactivity of haloalkanes is in the order I > Br > Cl > OTs. There are some differences between the two catalysts. Iodo, bromo, chloro, and tosyloxy compounds are reduced to give the alkylchromium reagents with chromium(II) chloride under B<sub>12</sub> catalysis, whereas the two latter compounds remain unchanged in the presence of CoPc. The cobalt-catalyzed reaction cannot be applied to tertiary and secondary alkyl iodides because of the low thermal stability of the carbon-chromium  $\sigma$  bond. In addition, the reaction with isobutyl iodide proceeds more slowly than that with an *n*-alkyl iodide.

Reduction of alkyl halides to the corresponding chromium reagents under mild conditions enables the Grignard-type reaction to proceed without protection of ketone and ester groups (Eq. 127). (51)

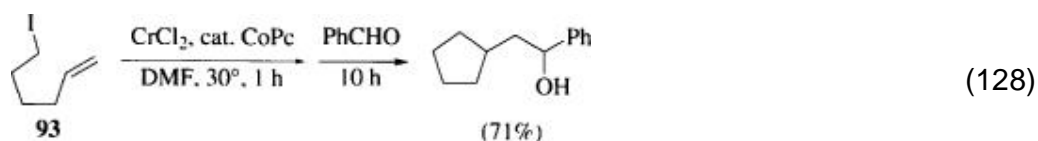


A possible mechanism for the formation of alkylchromium reagents under cobalt catalysis is shown in [Scheme 13](#). It involves 1) reduction of cobalt(III) or cobalt(II) into cobalt(I) by chromium(II), 2) nucleophilic substitution of an alkyl halide with cobalt(I) to give the alkylcobalt species **90**, 3) homolytic cleavage of the carbon-cobalt(III) bond to yield the alkyl radical **91** and cobalt(II), 4) reductive trapping of the alkyl radical **91** with chromium(II) to generate the alkylchromium **92** which then couples with an aldehyde, and 5) regeneration and recycling of cobalt(I) from cobalt(II) by chromium(II).

**Scheme 13.**

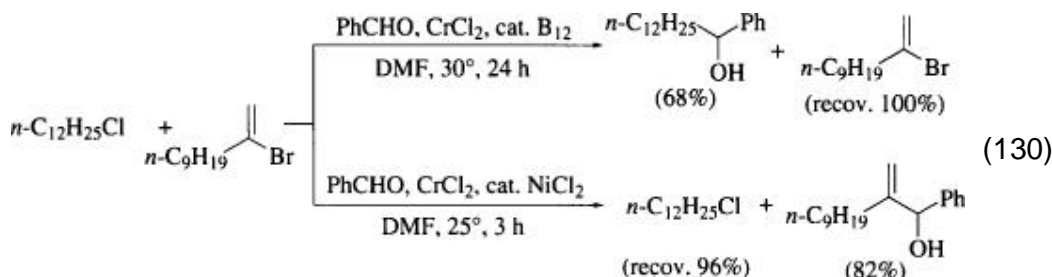
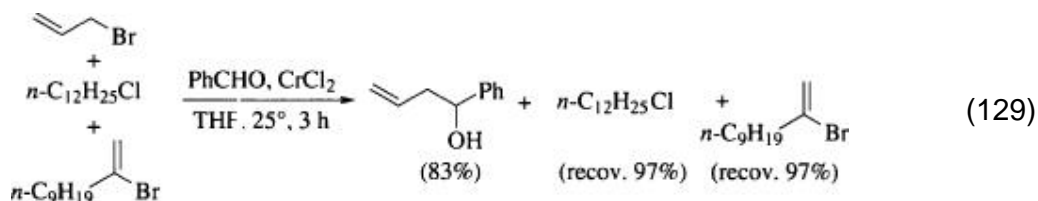


When 6-iodo-1-hexene (**93**) is used, the 5-hexenyl radical cyclizes to the corresponding cyclopentylmethyl radical that is trapped by chromium(II) before carbonyl addition occurs (Eq. [128](#)). (51)



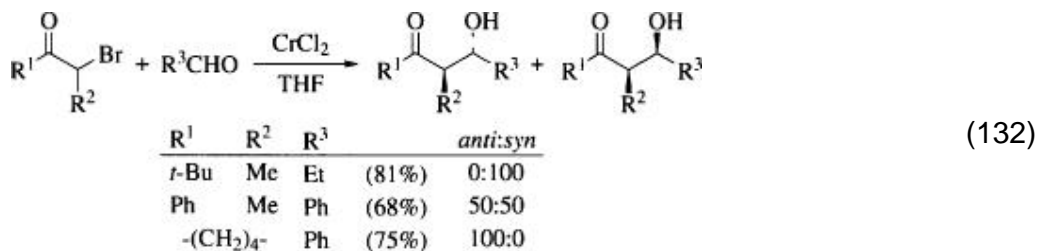
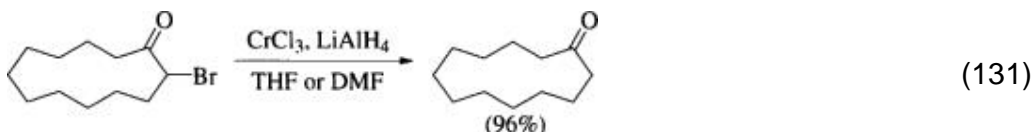
Organochromium reagents can be prepared chemoselectively by changing either the catalyst or the solvent. Alkenyl and alkyl halides remain unchanged under the conditions of allylchromium preparation. On the other hand, alkenyl-

and alkylchromium reagents are produced selectively under nickel and cobalt catalysis, respectively (Eqs. 129 and 130). (51)



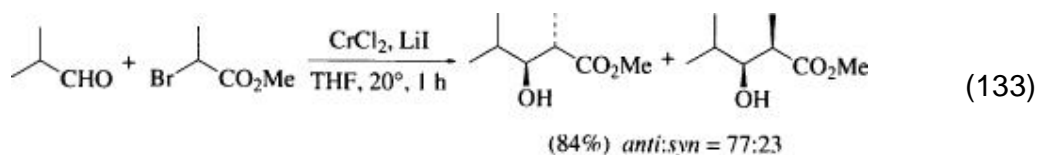
### 3.9. Chromium Enolates and Related Species

Reduction of  $\alpha$ -bromocyclododecanone with chromium(III) chloride and  $\text{LiAlH}_4$  in THF smoothly affords cyclododecanone in excellent yield (Eq. 131). (17) Attempts to trap the chromium enolate by addition of either iodomethane, trimethylsilyl chloride, or an aldehyde fails to give products of enolate functionalization. (35) In situ trapping with an aldehyde, however, can be accomplished and a mixture of anti and syn  $\beta$ -hydroxy ketones is produced (Eq. 132). (276) The isomer ratios depend on the structure of the  $\alpha$ -bromo ketones.

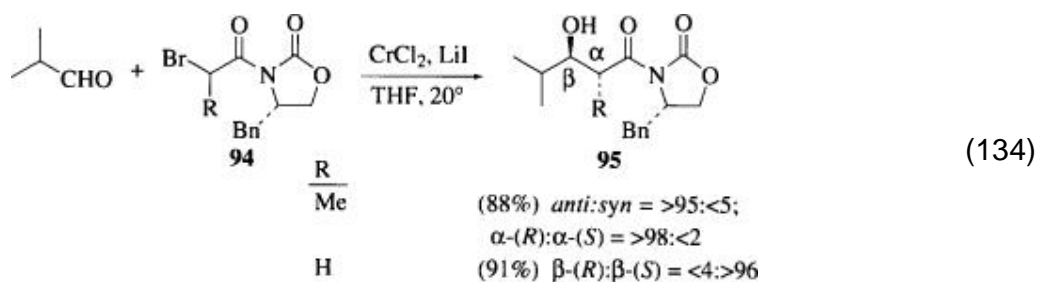




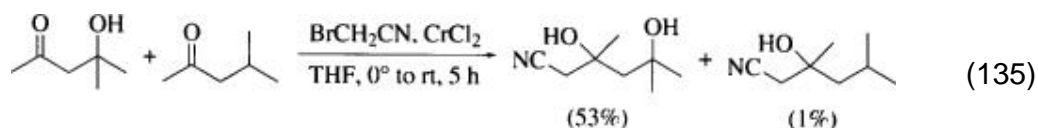
Reactions between  $\alpha$ -bromo esters and aldehydes proceed smoothly at 20 to 50° by addition of lithium iodide in THF to form anti adducts preferentially (Eq. 133). (277) The anti selectivity is in contrast to the syn selectivity obtained with lithium or zinc enolates of esters. A vinylogous  $\gamma$ -bromo ester adds to aldehydes and ketones only at the  $\alpha$  position of the ester. Similar to previously obtained organochromium reagents, chromium enolates of esters show aldehyde-selectivity (>50:1 vs. methyl ketone). (278, 279)



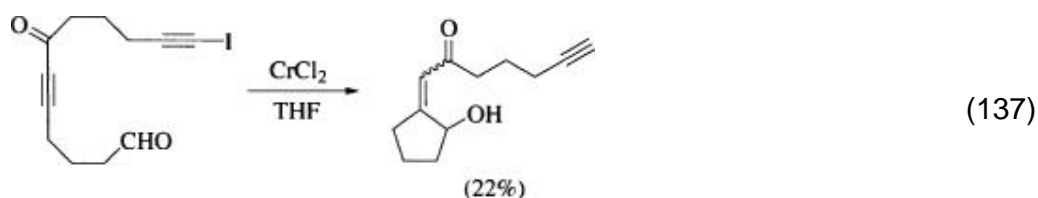
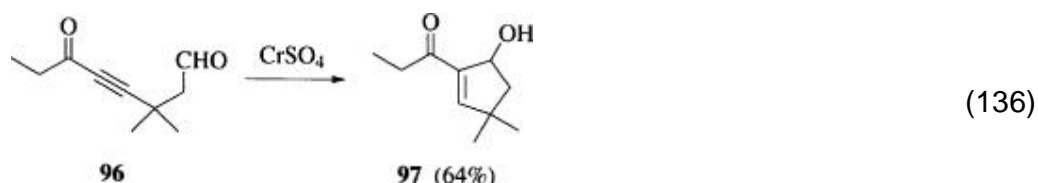
High diastereofacial selection is achieved with chiral *N*-acyloxazolidinones. Reactions with  $\alpha$ -alkyl substituted  $\alpha$ -bromoacyloxazolidinones **94** afford mainly anti adducts **95**, and chirality induction at the  $\alpha$  position of the anti isomers by the 4-substituted (*4 S*)-oxazolidinone is (R):(S) = >98:2. The selectivity is opposite to that with the boron enolate of the same chiral *N*-acyloxazolidinone (Eq. 134). (280, 281) Reactions of  $\alpha$ -bromoacetate having the (*4 S*)-oxazolidinone with aldehydes produce  $\beta$ -(*S*) adducts.



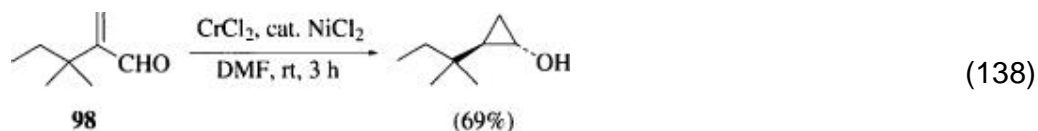
Chemoselective addition of a cyanoalkyl group to a  $\beta$ -hydroxy ketone proceeds smoothly via a chelate-accelerated pathway (Eq. 135). (109)



Enolate equivalents generated by reduction of acetylenic ketones **96** with chromium(II) sulfate react with the internal formyl group to form 5-membered  $\beta$ -hydroxy enones **97** in good yield (Eq. 136). (282) When the cyclization is difficult to promote at the  $\alpha$ -position of the acetylenic ketone, carbon-carbon bond formation occurs at the  $\beta$ -position (Eq. 137). (257)

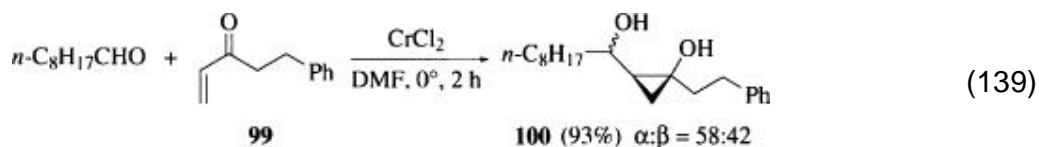


Reduction of  $\alpha$ ,  $\beta$ -unsaturated aldehydes **98** with chromium(II) chloride and a catalytic amount of nickel(II) chloride provides cyclopropanol derivatives in good yields (Eq. 138). (61) It has been proved, on the other hand, that the addition of the nickel salt is unnecessary, but water is indispensable to promote the cyclopropanol formation. (62) Trans isomers are selectively produced from  $\alpha$ - or  $\beta$ -substituted aldehydes. However, no reaction occurs in the case of unsaturated  $\alpha$ ,  $\beta$ -disubstituted aldehydes.

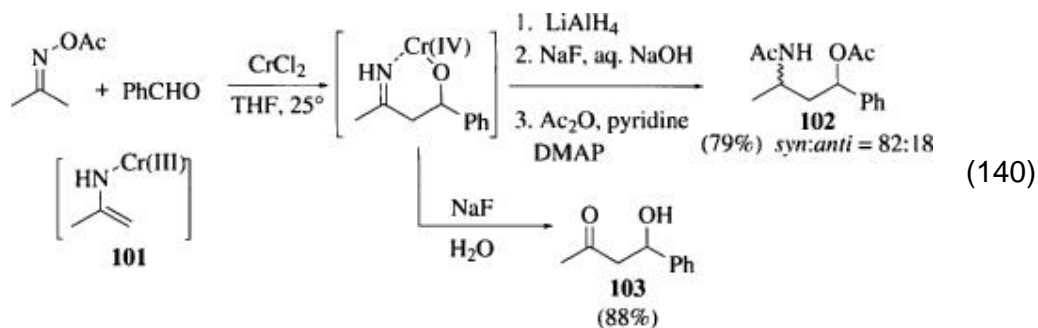


When the electron-transfer from chromium(II) to an  $\alpha$ ,  $\beta$ -unsaturated ketone **99** is conducted in the presence of an aldehyde under strictly water-free conditions, a cis 2-hydroxyalkyl-substituted cyclopropanol **100** is produced (Eq. 139). (62) The cyclopropanol is produced via an intermolecular aldol reaction of a radical enolate generated by the one-electron transfer to the enone from

chromium(II), followed by further one-electron reduction at the  $\beta$ -position of the enone and intramolecular cyclopropanol formation.



Enamine anion **101** is presumed to be produced by treating an *O*-acetyl oxime with chromium(II) chloride. (18, 68) Trapping of **101** with an aldehyde followed by reduction with lithium aluminum hydride produces a mixture of  $\beta$ -amino alcohols **102** in good yield (Eq. 140). Hydrolysis of the initial aldehyde adduct with aqueous sodium fluoride affords the  $\beta$ -hydroxy ketone **103**.



## 4. Comparison with Other Methods

Because the processes outlined in this chapter are fundamental, numerous other methods have been developed to achieve the same transformations. Here an attempt is made to compare some of the typical chromium-mediated reactions to other methods for accomplishing these reactions.

### 4.1. Addition of Allylic Metals to Carbonyl Compounds

Many different allylmetal reagents have been studied because of their high reactivities, selectivities, and ease of preparation. (283-285) Among those reported, the allylmetal reagents listed below are frequently employed for synthesis of complex molecules. Diastereoselectivity that arises by induction by the aldehyde (or ketone) stereocenters, such as Cram and anti-Cram selectivity, will not be discussed here, because the selectivity largely depends on the structure and configuration of the carbonyl components.

For simple allylation of carbonyl compounds, two types of reagents are frequently employed due to their ease of handling. The first type are commercially available compounds that can be stored, such as allyltrimethylsilane, (286-288) which is used in combination with Lewis acids such as titanium tetrachloride and tin tetrachloride. The other type are the reagents prepared in situ from allylic halides and low-valent metals. Allylzinc, (289) allyltin, (290, 291) allylaluminum, (292, 293) and allylindium compounds (294-296) are typical examples, and are prepared by reduction of allyl bromide (chloride or iodide) with zinc, tin (or tin(II) chloride), aluminum and lead(II) bromide (cat), and indium(0) (or indium(I) iodide), respectively. The allylchromium reagents mentioned in this chapter are included in this category. When metal powder is employed as a reductant, activation of the metal is sometimes necessary to obtain reproducible results. Addition of a catalytic amount of iodine or chlorotrimethylsilane, or ultrasonic irradiation (297) is sometimes effective for this purpose.

In the case of crotylmetal reagents, problems in controlling regio- ( $\alpha$  /  $\gamma$  selectivity) and stereochemistry (syn/anti selectivity) arise. (284) Although several crotyl-type reagents are reported to add to carbonyl compounds at the  $\alpha$  -position, (114, 298, 299) most of the reagents add at the  $\gamma$  -position via allylic transposition from the less-sterically demanding crotylmetal species. There are two types of  $\gamma$  -position-oriented reagents. The first type adds aldehydes in a stereospecific manner; allylic boranes and boronates typical examples in this category. (300, 301) The important feature of crotyl boronates (or boranes) is their slow rate of allylic equilibration (the crotylboronates are in fact configurationally stable), which enables the preparation of configurationally fixed allylboronates. Addition of allylic boronates to carbonyl compounds proceeds in a stereospecific manner via a six-membered chair-like

transition state, thus, the syn/anti diastereoselectivity can be controlled by the preparation of geometrically defined allylic boronates.

The second type of reagent produces adducts in a stereoconvergent manner. Crotylchromium reagents described in this chapter are one of the typical examples. The anti-selectivity of the reagents stems both from a fast equilibration of the crotylchromium species and a six-membered cyclic transition state, where both substituents possess equatorial positions. Lewis acid catalyzed addition of crotyltrialkylstannanes to aldehydes proceeds, however, with syn selectivity. (290) The acidcatalyzed reactions with aldehydes proceed via an extended transition state and, therefore, the stereoselectivity of the reactions does not depend on the stereochemistry of the crotyltrialkylstannanes.

There are many approaches to achieve asymmetric allylations. Stereodefined homoallylic alcohols can be prepared with allylic boronates having asymmetric diol ligands. (302-305) Catalytic asymmetric allylation reactions with allylsilanes (306, 307) and -stannanes (308-310) have made considerable progress. Allylaluminum, tin(II) triflate, and a chiral diamine ligand also produces chiral homoallylic alcohols. In contrast, reagent-control asymmetric induction with chiral ligands on chromium(II) is a continuing problem. (16, 132-135)

Chromium(II) mediated reactions require water-free conditions. However, several allylic metal reagents, especially allylic indium (297, 311, 312) and tin reagents, (313) can be used in aqueous media. Tetraallyltin shows high chemoselectivity. (313)

#### **4.2. Addition of Alkenylmetals to Carbonyl Compounds**

Alkenylmetal reagents are usually prepared by 1) reduction of alkenyl halides with low-valent metals (314) or alkylolithium compounds, (315, 316) 2) hydro- or carbometallation of acetylenes, and 3) Shapiro reaction from ketones. (317)

Reduction of alkenyl halides with magnesium leading to alkenyl Grignard reagents and iodine-metal exchange from alkenyl iodides with butyllithium are typical examples of the first category. An easy preparation of alkenyllithium reagents from the corresponding alkenyl iodides with *n*-butyllithium at room temperature has appeared recently. (318) One of the problems in employing these reagents is controlling the chemoselectivity of the reactions of alkenylmetal reagents.

In the second category, hydroboration and -aluminum have been employed extensively in the preparation of alkenylmetal reagents. However, the reactivity of the alkenylboron and -aluminum species toward carbonyl compounds is not high even when they are converted into the corresponding ate complexes.

Thus, the alkenylboron and -aluminum species are usually converted into the corresponding halides with electrophilic sources of halogen (iodine or *N*-bromosuccinimide), and metalated as mentioned above. (319, 320) The boron species can also be transformed to the corresponding zinc species by treatment with diethylzinc. (321) Hydro- and carbonyl-zincation of terminal acetylenes have been developed, and the alkenylzirconium compounds are used by either transmetallation (322) or activation with silver(I) salts. (323)

Compared to the above reagents, alkenylchromium reagents have the advantage of easy preparation, especially when the substrates have many oxygen functionalities. The alkenylchromium reagents also have moderate nucleophilicity, which enables aldehyde-selective addition.

### 4.3. Addition of Alkynylmetals to Carbonyl Compounds

There are three typical routes to obtain alkynyl metal reagents: 1) deprotonation of 1-alkynes with appropriate bases; 2) preparation from 1-alkynylsilanes or 1-alkynylstannanes; and 3) reduction of 1-halo-1-alkynes.

Many alkynylmetals, such as alkynylboron, (324) -aluminum, -cerium, (325) and -manganese compounds, (326) are prepared by transmetallation from the corresponding alkali or alkali-earth acetylides. Such alkynylmetals as alkynyllithium, -sodium, and -magnesium compounds are easily generated by treatment of the corresponding 1-alkynes with alkylmetals or metal amides, and are generally used in situ for preparation of propargylic alcohols by reaction with carbonyl compounds. Due to the strong basicity of the alkylmetals and metal amides, base-induced side reactions sometimes follow. Although intramolecular cyclization between an alkynylmetal and an aldehyde can be accomplished with lithium or sodium hexamethyldisilazide, (327, 328) milder preparation of alkynyl metals is desirable, especially when electrophilic functionalities exist in the same molecule. Several improved methods appear to overcome this difficulty. One of the superior reagents is a combination of tin(II) triflate (or tin(IV) chloride) and amine in dichloromethane. (329)

Reactions of alkynylsilanes or -stannanes with carbonyl compounds usually proceed under mild conditions. It should be noted that the alkynylsilanes can be employed using either fluoride ion (330) or Lewis acid (331) catalyzed conditions.

Asymmetric addition of boron and zinc acetylide, generated in situ, to aldehydes has been achieved. (332-334)

Alkynylchromium reagents are prepared in situ by reduction of 1-halo-1-alkynes with chromium(II) under mild conditions. The 1-iodo-1-alkyne reactants are prepared by treatment of 1-alkynes with butyllithium and iodine in

tetrahydrofuran or under milder conditions with morpholine and iodine in benzene. (335)

#### 4.4. E Olefin Formation from Aldehydes

There are several predictable methods to obtain E 1-halo-1-alkenes: 1) formal addition of hydrogen iodides (or bromides) to 1-alkynes, e.g., hydroboration, (319) -aluminum, (320) and -zirconation (336, 337) of 1-alkynes followed by trapping with electrophiles, such as iodine or *N*-bromosuccinimide, and 2) treatment of stereodefined alkenylsilanes or alkenylstannanes with iodine or *N*-bromosuccinimide. In the case of E 1-chloro-1-alkenes, partial reduction of 1-chloro-1-alkynes with lithium aluminum hydride can be employed. (338) Compared to these methods, the chromium method is mild enough to be used with highly functionalized substrates, and in addition, the carbon chain increased by one carbon to directly afford E 1-halo-1-alkenes from aldehydes.

In contrast to Z olefins, which can be prepared from aldehydes with non-stabilized phosphorus ylides (Wittig reagents) under lithium salt-free conditions, (339) E olefins are rather difficult to prepare selectively. Selective preparation of E olefins is accomplished by a  $\beta$ -oxido ylide method. (340) Julia olefination also affords E olefins with high levels of selectivity. (341, 342) Peterson elimination from a single  $\beta$ -hydroxy silane diastereomer gives both E and Z alkenes selectively depending on the elimination conditions employed. (343) Transition metal catalyzed coupling of 1-halo-1-alkenes with organometallic species also produces olefins stereoselectively. (344-346)

Due to the considerable utility of alkenylsilanes as synthetic intermediates, many methods have been developed for the preparation of E 1-trimethylsilyl-1-alkenes: (347, 348) 1) hydrosilylation of 1-alkynes; (349, 350) 2) Me<sub>3</sub>SiCl-trapping of alkenylmetal compounds derived from metallation of E 1-halo-1-alkenes; (351) or 3) hydrometallation of 1-alkynes. Reactions between metal salts of bis(trimethylsilyl)methane and aldehydes occur smoothly to produce alkenylsilanes; however, it is difficult to control the stereochemistry of the products. In addition, yields are rather low in the case of enolizable aldehydes due to the strong basicity of the reagents. (352, 353)

E Alkenylstannanes and -boronates are usually prepared from the corresponding 1-alkynes. (354-356) The preparative method from aldehydes summarized in this chapter using the chromium reagents is useful from the viewpoint of the reactants.

There are many methods for methylenation of aldehydes, e.g., using Wittig reagents, silicon-based reagents, (357, 358) the Tebbe reagent (359) or the Petasis reagents, (359) or a combination of dibromomethane, zinc, lead(II) chloride (cat.), and titanium(IV) chloride. (360, 361) Among these, a combination of diiodomethane, zinc, lead(II) chloride (cat), and

trimethylaluminum (or titanium(IV) tetraisopropoxide), (362, 361) and the combination of diiodomethane and chromium(II) chloride (7) are methods that can be conducted under mild conditions.

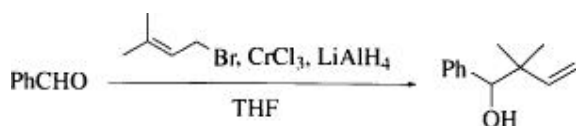


## 5. Experimental Conditions

Pure chromium(II) chloride is a light gray, air sensitive compound. Commercial samples of chromium(II) chloride powder are sometimes light greenish gray in color due to partial oxidation and normally can be used without further purification. All manipulations involving chromium(II) chloride and the chromium(III) chloride lithium aluminum hydride system must be carried out in an inert atmosphere of argon or nitrogen. The salt is usually transferred using a glovebag (or glovebox) and the reactions are conducted using the standard benchtop techniques for handling of air-sensitive materials: the vessel is connected with an inert gas line or simply with a balloon of butadiene-rubber. Chromium(III) chloride and nickel(II) chloride are hygroscopic and should also be handled under a dry, inert atmosphere. Chloro- and iodotrimethylsilane are distilled before use. Lithium iodide and sodium iodide are dried at 150° in vacuo (0.1 Torr) for 2 hours. Commercial samples of CrCl<sub>3</sub>(thf)<sub>3</sub>, (363) vitamin B<sub>12</sub>, and zinc and manganese metal powders are used without further purification. Tetrahydrofuran (THF) and 1,4-dioxane are distilled from sodium and benzophenone just before use. Dimethylformamide (DMF) is heated at reflux in the presence of calcium sulfate under reduced pressure and distilled with nitrogen bubbling from a capillary (bp 76°, 39 Torr). Commercially available anhydrous purified THF, dioxane, and DMF can be used as solvents without further purification. 1,3-Dimethyltetrahydro-2(1*H*)-propyleneurea (DMPU) is freshly distilled over calcium hydride.

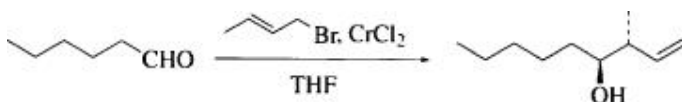
While the specific compounds cannot be identified, there is evidence that certain chromium compounds cause cancer in humans. All chromium compounds are regulated by the EPA, but no specific data are available to link trivalent chromium to cancer. Prudent judgment dictates that exposure should be minimized as much as possible. The aqueous layers from chromium-mediated reactions and any other waste materials should be disposed in accordance with all applicable federal, state, and local environmental regulations.

## 6. Experimental Procedures



### 6.1.1.1. 2,2-Dimethyl-1-phenyl-3-buten-1-ol (Addition of an Allylic Chromium Reagent Derived from an Allylic Bromide and Chromium(III) Chloride-Lithium Aluminum Hydride to an Aldehyde) (5)

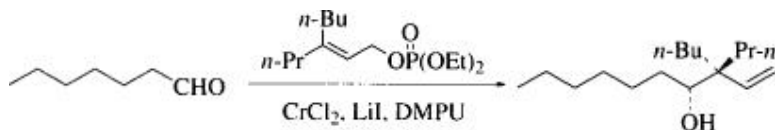
To a suspension of chromium(III) chloride (0.79 g, 5.0 mmol) in THF (10 mL) at  $0^\circ$  was added portionwise lithium aluminum hydride (95 mg, 2.5 mmol). Gas immediately evolved with darkening of the initial purple solution which finally turned dark brown. After gas evolution had ceased, benzaldehyde (0.21 g, 2.0 mmol) and a solution of 1-bromo-3-methyl-2-butene (0.37 g, 2.5 mmol) in tetrahydrofuran (10 mL) were added successively at  $25^\circ$  to the low-valent chromium reagent. After 2 hours, the reaction mixture was mixed with water (10 mL) and thoroughly extracted with ether. The extracts were washed with saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated. Distillation of the residue at  $105\text{--}110^\circ$  (bath temp)/0.12 Torr gave 0.27 g (82%) of the product.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  0.94 (s, 3H), 0.99 (s, 3H), 1.5–1.8 (br s, 1H), 4.34 (s, 1H), 4.8–6.2 (m, 3H), 7.26 (s, 5H); IR (neat) 3425, 3095, 3075, 3035, 1638, 1605, 1490, 1020, 1000, 915, 730, 702  $\text{cm}^{-1}$ .



### 6.1.1.2. anti-3-Methyl-1-nonen-4-ol (Addition of a Crotylchromium Reagent Derived from Crotyl Bromide and Chromium(II) Chloride to an Aldehyde) (105)

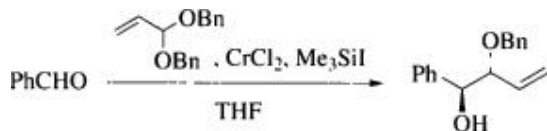
To anhydrous chromium(II) chloride (9.8 g, 80 mmol) at  $0^\circ$  was added dry THF (100 mL) with vigorous stirring under an argon atmosphere. The salt partially dissolved in a slightly exothermic process. To the suspension was added 1-hexanal (2.0 g, 20 mmol) at  $0^\circ$  and 1-bromo-2-butene (5.4 g, 40 mmol) in THF (40 mL). The mixture was stirred at  $0^\circ$  for 5 hours and the reaction was monitored by TLC (ethyl acetate-hexane, 1:5). The mixture was poured into ice-cold water (400 mL) and extracted with ether ( $3 \times 100$  mL). The combined extracts were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated. The crude product was purified

by column chromatography on silica gel (ethyl acetate-hexane, 1:20) to give 2.6 g (84%) of the product (anti:syn = 96:4).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  0.92 (t,  $J = 7.5$  Hz, 3H), 1.04 (d,  $J = 6.6$  Hz, 3H), 1.0–1.6 (m, 8H), 1.80 (br s, 1H), 2.0–2.4 (m, 1H), 3.2–3.5 (m, 1H), 5.01 (dd,  $J = 2.7, 17.1$  Hz, 1H), 5.18 (dd,  $J = 2.7, 10.8$  Hz, 1H), 5.6–5.9 (m, 1H); IR (neat) 3380, 1638, 1260, 1081, 1001, 911  $\text{cm}^{-1}$ .



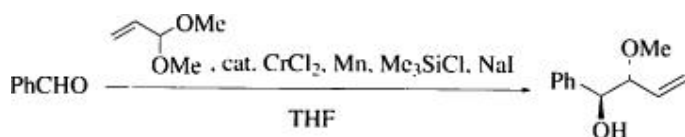
6.1.1.3. (5*R*\*,6*R*\*)-5-Ethenyl-5-propyldodecan-6-ol (Chromium(II)-Mediated Stereodivergent Addition of an Allylic Phosphate to an Aldehyde) (115)

A mixture of dried lithium iodide (0.16 g, 1.2 mmol) and anhydrous chromium(II) chloride (1.2 g, 10 mmol) in 1,3-dimethyltetrahydro-2(1*H*)-propyleneurea (DMPU, 5 mL) was stirred at 25° for 15 minutes. A solution of diethyl (*Z*)-3-propyl-2-heptenyl phosphate (1.5 g, 5.0 mmol) and heptanal (0.46 g, 4.0 mmol) in DMPU (2 mL) was added and the mixture was stirred at 25° for 3–6 hours. The reaction was quenched with 200 mL of saturated aqueous ammonium chloride. The organic phase was washed with several 100 mL portions of saturated aqueous ammonium chloride, and the aqueous phase was extracted several times with 100 mL of ether. The combined organic phase was dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvents, the residual oil was purified by flash chromatography (3% ether in hexanes) leading to 0.91 g (90%) of the product [(5*R*\*,6*R*\*):(5*S*\*,6*R*\*) = 99:1].  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  0.80–0.87 (m, 6H), 1.07–1.37 (m, 20H), 1.44–1.53 (m, 4H), 3.33 (d, 1H,  $J = 9.9$  Hz), 4.95 (d, 1H,  $J = 17.8$  Hz), 5.13 (d, 1H,  $J = 11.1$  Hz), 5.66 (dd, 1H,  $J = 11.1, 17.8$  Hz);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  14.0, 14.1, 15.0, 22.7, 23.7, 25.7, 27.0, 29.1, 29.4, 31.9, 32.0, 32.6, 34.8, 46.8, 75.9, 114.8, 143.1; IR (neat) 3442, 2962, 2940, 1645, 1486  $\text{cm}^{-1}$ . The (5*S*\*,6*R*\*) isomer was also prepared from diethyl (*E*)-3-propyl-2-heptenyl phosphate in 64% yield [(5*S*\*,6*R*\*):(5*R*\*,6*R*\*) = 97:3].  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  0.80–0.87 (m, 6H), 1.09–1.48 (m, 24H), 3.33 (d,  $J = 10.4$  Hz, 1H), 4.93 (d,  $J = 17.8$  Hz, 1H), 5.11 (d,  $J = 11.1$  Hz, 1H), 5.65 (dd,  $J = 11.1, 17.8$  Hz, 1H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  14.1, 14.2, 15.1, 16.8, 22.7, 23.7, 25.6, 27.0, 29.4, 32.0, 32.1, 32.7, 35.3, 46.8, 75.9, 114.9, 143.1; IR (neat) 3452, 2970, 1482  $\text{cm}^{-1}$ . Diastereomeric ratios were determined by comparing the two signals at 34.8 and 35.3 ppm by  $^{13}\text{C NMR}$  spectroscopy.



6.1.1.4. *anti*-2-Benzyloxy-1-phenyl-3-buten-1-ol (Addition of an  $\alpha$ -Alkoxyallylic Chromium Reagent to an Aldehyde) (158)

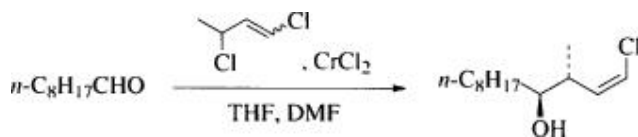
A suspension of chromium(II) chloride (0.74 g, 6.0 mmol) in THF (14 mL) was cooled to  $-30^{\circ}$ , and to the suspension was added successively a solution of acrolein dibenzyl acetal (0.51 g, 2.0 mmol) in THF (3 mL), iodotrimethylsilane (2.0 mL of a 1.0 M hexane solution, 2.0 mmol), and a solution of benzaldehyde (0.11 g, 1.0 mmol) in THF (3 mL). The color of the mixture gradually turned from gray to brownish red. After being stirred at  $-30^{\circ}$  for 3 hours, the mixture was poured into 1.0 M hydrochloric acid (15 mL) and extracted with ether (3  $\times$  15 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. Purification of the crude product by column chromatography on silica gel (ethyl acetate-hexane, 1:10) afforded 0.25 g (98%, *anti*:*syn* = 88:12) of the product. *Anti* isomer:  $R_f$  = 0.35 (ethyl acetate-hexane, 1:5);  $^1\text{H NMR}$  (  $\text{CDCl}_3$ )  $\delta$  2.58 (d,  $J$  = 4 Hz, 1H), 3.96 (dd,  $J$  = 5, 8 Hz, 1H), 4.38 (d,  $J$  = 12 Hz, 1H), 4.63 (d,  $J$  = 12 Hz, 1H), 4.85 (dd,  $J$  = 4, 5 Hz, 1H), 5.2–5.4 (m, 2H), 5.76 (ddd,  $J$  = 8, 11, 17 Hz, 1H), 7.2–7.5 (m, 10H); IR (neat) 3440, 3028, 2864, 1454, 1199, 1067, 930, 698  $\text{cm}^{-1}$ . *Syn* Isomer:  $R_f$  = 0.40 (ethyl acetate-hexane, 1:5);  $^1\text{H NMR}$  (  $\text{CDCl}_3$ )  $\delta$  3.23 (d,  $J$  = 2 Hz, 1H), 3.88 (dd,  $J$  = 7, 8 Hz, 1H), 4.40 (d,  $J$  = 11 Hz, 1H), 4.58 (dd,  $J$  = 2, 8 Hz, 1H), 4.69 (d,  $J$  = 12 Hz, 1H), 5.1–5.3 (m, 2H), 5.65 (ddd,  $J$  = 3, 7, 10 Hz, 1H), 7.2–7.4 (m, 10H).



6.1.1.5. *anti*-2-Methoxy-1-phenyl-3-buten-1-ol (Addition of an  $\alpha$ -Alkoxyallylic Chromium Reagent to an Aldehyde - A Catalytic Version) (161)

Anhydrous chromium(II) chloride (13.6 mg, 0.110 mmol), manganese(0) powder (0.143 g, 2.55 mmol), and sodium iodide (46.0 mg, 0.307 mmol) were placed in a flame-dried 25-mL flask under a nitrogen (or argon) atmosphere. To the flask was added THF (7 mL) by syringe, and the resulting suspension was stirred for 20 minutes prior to cooling to  $-25^{\circ}$  to  $-30^{\circ}$ . Sequentially via syringe, chlorotrimethylsilane (0.600 mL, 4.75 mmol) which had been purified

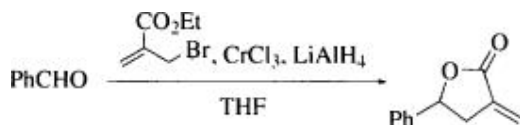
immediately before use by passage through a plug of basic alumina under argon, acrolein dimethyl acetal (0.400 mL, 3.38 mmol), and benzaldehyde (159 mg, 1.50 mmol) were added each in one portion. The resulting light green reaction mixture was stirred for 12 hours at  $-25^{\circ}$  to  $-30^{\circ}$  during which time the color faded and a precipitate of sodium chloride appeared in some cases. The reaction mixture was then treated with aqueous hydrochloric acid (1 M, 5 mL), warmed to room temperature, and the dark green aqueous phase extracted with ether ( $3 \times 15$  mL). The combined organic phases were washed with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford 231 mg (88%) of a nearly pure mixture of *anti*- and *syn*-2-methoxy-1-phenyl-3-buten-1-ols as a yellow/tan oil. The anti:*syn* ratio of the diastereomeric alcohols was determined by capillary GC (5% MePh Silicone) and found to be 10.9:1 (anti:*syn*) by comparison with an authentic mixture prepared independently. The crude product could be further purified by chromatography on silica gel to afford the pure mixture (anti:*syn* = 10.9:1) of 2-methoxy-1-phenyl-3-buten-1-ols having the following spectroscopic characteristics: IR (film) 3444, 3030, 2982, 2932, 2823, 1494, 1452, 1422, 1333, 1189, 1102  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ): *anti* diastereomer:  $\delta$  2.6 (d,  $J = 3.5$  Hz, 1H), 3.35 (s, 3H), 3.79 (dd,  $J_1 = 7.7$  Hz,  $J_2 = 4.5$  Hz, 1H), 4.85 (t,  $J = 4$  Hz, 1H), 5.20 (d,  $J = 17$  Hz, 1H), 5.29 (d,  $J = 9.9$  Hz, 1H), 5.70–5.61 (m, 1H), 7.377.28 (m, 5H); *syn* diastereomer:  $\delta$  2.55 (m, 1H), 3.40 (s, 3H), 3.65 (m, 1H), 4.54 (m, 1H), 5.10 (d,  $J = 17$  Hz, 1H), 5.20 (d,  $J = 12$  Hz, 1H), 5.62–5.50 (m, 1H), 7.37–7.28 (m, 5H).



#### 6.1.1.6. *anti*-(*Z*)-1-Chloro-3-methyl-1-dodecen-4-ol [Addition of a (*Z*)- $\gamma$ -Chloroallylic Anion Synthon to an Aldehyde] (163)

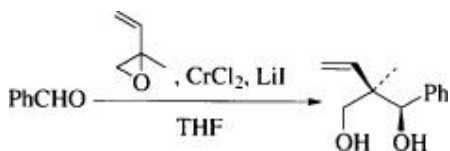
To chromium(II) chloride (0.49 g, 4.0 mmol) under an argon atmosphere was added THF (6 mL) and the suspension was stirred for 15 minutes. To this suspension was added 3 mL of dimethylformamide and the mixture was stirred for another 30 minutes. To this yellowish green suspension was added dropwise a solution of nonanal (0.14 g, 1.0 mmol) and 1,3-dichloro-1-butene (0.25 g, 2.0 mmol) in a mixed solvent of THF and DMF (2:1, 1.8 mL). The color of the mixture gradually turned dark brown. After being stirred at  $25^{\circ}$  for 1 hour, the mixture was poured into saturated sodium chloride (15 mL) and extracted with ether ( $3 \times 15$  mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated. Purification of the crude product by column chromatography on silica gel (ethyl acetate-hexane,

1:5 ~ 1:10) afforded 0.20 g (88%) of the product (Z:E = 95:5, anti:syn = 99:1).  $^1\text{H NMR}$  (  $\text{CDCl}_3$ )  $\delta$  0.99 (t,  $J = 7.5$  Hz, 3H), 1.06 (d,  $J = 6.9$  Hz, 3H), 1.1–1.6 (m, 15H), 2.75–2.95 (m, 1H), 3.4–3.6 (m, 1H), 5.75 (dd,  $J = 7.1, 9.6$  Hz, 1H), 6.11 (d,  $J = 7.1$  Hz, 1H).



6.1.1.7.  $\alpha$ -Methylene- $\gamma$ -phenyl- $\gamma$ -butyrolactone (Addition of a 2-Alkoxyacryloyl-Substituted Allylic Chromium Reagent to an Aldehyde) (148)

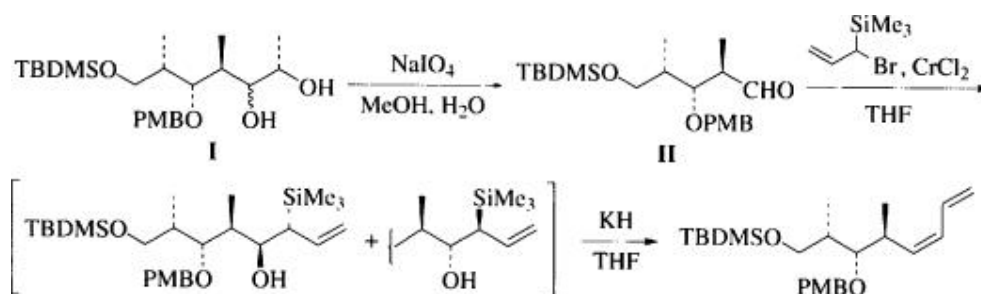
Lithium aluminum hydride (76 mg, 2.0 mmol) was added portionwise to a suspension of chromium(III) chloride (0.63 g, 4.0 mmol) in THF (5 mL) at  $0^\circ$  under an argon atmosphere. Immediate gas evolution occurred with darkening of the initial purple color, which finally turned dark brown. After the gas evolution had ceased, the reaction mixture was stirred for an additional 15 minutes at  $25^\circ$ . A solution of benzaldehyde (0.11 g, 1.0 mmol) in THF (5 mL) was added in one portion, then a solution of ethyl  $\alpha$ -(bromomethyl)acrylate (0.38 g, 2.0 mmol) in THF (5 mL) was added dropwise over 10 minutes. The resulting mixture was stirred at  $25^\circ$  for 3 hours and poured into ice cold water. The organic layer was separated and the rest was extracted with ether ( $4 \times 10$  mL). The combined ethereal extracts were washed with aqueous hydrochloric acid (1.0 M) and brine, dried over anhydrous magnesium sulfate, and concentrated. Purification of the product by thin layer chromatography on silica gel gave 0.16 g (94%) of the butyrolactone as a colorless oil. IR (  $\text{CCl}_4$ )  $1800, 1674, 700$   $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (  $\text{CCl}_4$ ):  $\delta$  2.65–2.96 (m, 1H), 3.22–3.53 (m, 1H), 5.44 (t,  $J = 3$  Hz, 1H), 6.22 (t,  $J = 3$  Hz, 1H), 7.27–7.43 (m, 5H).



6.1.1.8. (1*R*\*,2*R*\*)-1-Phenyl-2-methyl-2-ethenyl-1,3-propanediol (Addition of a  $\delta$ -Alkoxyallylic Chromium Reagent Generated from a 1,3-Diene Monoepoxide to an Aldehyde) (152)

To chromium(II) chloride (0.49 g, 4.0 mmol) was added THF (12 mL) at  $0^\circ$  under an argon atmosphere, and the pale green suspension was stirred at  $0^\circ$  for 1 hour. To the suspension was added successively at  $0^\circ$  a solution of isoprene oxide (0.17 g, 2.0 mmol) in THF (2 mL), lithium iodide (1.0 M solution

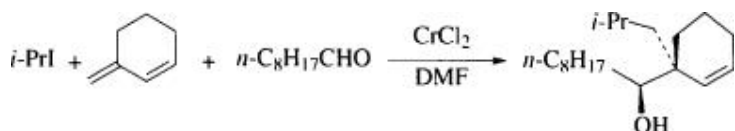
in THF, 2.0 mL), and a solution of benzaldehyde (0.11 g, 1.0 mmol) in THF (2 mL). After being stirred at 0° for 1 hour, the mixture was poured into a mixture of saturated sodium chloride solution, water, and ether (1:1:1, 75 mL) and the whole mixture was stirred vigorously at 25° for 15 hours. The organic layer was separated and the rest was extracted with ether (4 × 10 mL). The combined ethereal extracts were dried over anhydrous magnesium sulfate and concentrated. Purification of the crude product by column chromatography [ethyl acetate-hexane, 1:2] gave 1-phenyl-2-methyl-2-vinyl-1,3-propanediol in 95% yield (0.18 g, (1*R*\*,2*R*\*):(1*R*\*,2*S*\*) = 98:2); bp 130° (bath temp, 0.3 Torr); IR (neat): 3318, 2964, 2922, 2876, 1638, 1454, 1022, 917, 728, 700 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ 0.80 (s, 3H), 3.00–3.75 (bs, 2H), 3.41 (d, *J* = 12 Hz, 1H), 3.53 (d, *J* = 12 Hz, 1H), 4.57 (s, 1H), 4.90 (dd, *J* = 18, 1 Hz, 1H), 5.10 (dd, *J* = 11, 1 Hz, 1H), 5.93 (dd, *J* = 18, 11 Hz, 1H), 7.13–7.33 (m, 5H).



6.1.1.9. (*Z*)-(2*S*,3*S*,4*S*)-1-(*t*-Butyldimethylsilyloxy)-3-(*p*-methoxybenzyloxy)-2,4-dimethyl-5,7-octadiene (Formation of a (*Z*)-Terminal 1,3-Diene via an *anti*-2-Trimethylsilyl-3-buten-1-ol) (157)

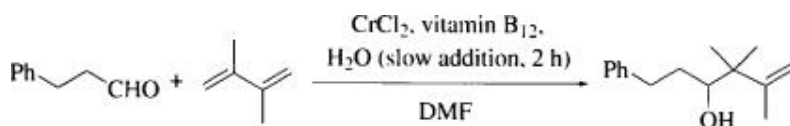
The aldehyde **II**, derived by oxidative cleavage of the 1,2-diol **I** (2.00 g, 4.69 mmol) with sodium periodate (3.7 g, 18.2 mmol) in methanol (70 mL) and water (35 mL), and 1-bromo-1-trimethylsilyl-2-propene (5.34 g, 28.1 mmol) were dissolved in THF (20 mL). The solution was added to a suspension of chromium(II) chloride (6.30 g, 51.6 mmol) in THF (35 mL), and the mixture was stirred at room temperature for 20 hours. The resultant deep purple suspension was partitioned between pH 7 buffer (100 mL) and ethyl acetate (3 × 250 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was dissolved in THF (35 mL) and added via cannula to a stirred suspension of potassium hydride [2.50 g of 35 wt% suspension, 42.2 mmol, washed with hexane (3 × 15 mL)] in THF (35 mL) at 0°. The mixture was allowed to warm to room temperature and after 2 hours the brown suspension was cannulated into ice (100 mL) and extracted with ether (3 × 200 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification of the crude product by flash chromatography (5% ethyl

acetate-hexane) gave the title diene as a colorless oil (1.87 g, 98%):  $R_f = 0.43$  (20% ethyl acetate-hexane);  $[\alpha]_D^{25} + 58.4$  (c 0.6,  $\text{CHCl}_3$ ). IR (Thin film) 2956 (vs), 2930 (vs), 2857 (s), 1613 (m), 1514 (vs)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.03 (s, 3H), 0.04 (s, 3H), 0.91 (s, 9H), 0.92 (d,  $J = 7.0$  Hz, 3H), 1.00 (d,  $J = 6.8$  Hz, 3H), 1.871.78 (m, 1H), 2.93 (ddq,  $J = 9.9, 6.7, 6.6$  Hz, 1H), 3.38 (dd,  $J = 5.9, 4.6$  Hz, 1H), 3.45 (dd,  $J = 9.8, 6.0$  Hz, 1H), 3.52 (dd,  $J = 9.8, 6.8$  Hz, 1H), 3.79 (s, 3H), 4.44 (d,  $J = 10.7$  Hz, 1H), 4.53 (d,  $J = 10.7$  Hz, 1H), 5.08 (d,  $J = 10.1$  Hz, 1H), 5.18 (d,  $J = 16.8$  Hz, 1H), 5.51 (dd,  $J = 10.4, 10.4$  Hz, 1H), 6.01 (dd,  $J = 11.0, 11.0$  Hz, 1H), 6.65 (ddd,  $J = 16.8, 10.8, 10.4$  Hz, 1H), 6.84 (d,  $J = 8.6$  Hz, 2H), 7.24 (d,  $J = 8.5$  Hz, 2H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.0, 135.9, 132.8, 131.5, 129.3, 128.9, 117.0, 113.6, 83.0, 74.4, 65.6, 55.2, 38.7, 35.6, 26.0, 18.4, 18.3, 11.6, -5.3, -5.4.



6.1.1.10. (1*S*\*,1'*R*\*)-1-(1'-Isobutyl-2'-cyclohexenyl)nonan-1-ol (A Three-Component Coupling Reaction of an Iodoalkane, a 1,3-Diene, and an Aldehyde) (50)

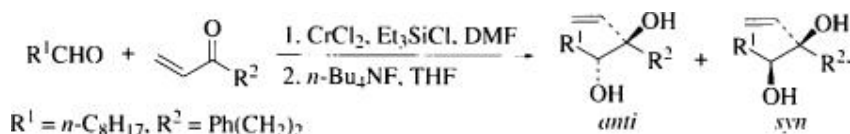
To a mixture of  $\text{CrCl}_2$  (0.49 g, 4.0 mmol) in dry, oxygen-free DMF (7 mL) was added a solution of nonanal (0.14 g, 1.0 mmol), 3-methylenecyclohexene (0.19 g, 2.0 mmol), and isopropyl iodide (0.34 g, 2.0 mmol) in DMF (3 mL) at  $25^\circ$ . After being stirred at  $25^\circ$  for 24 h, the reaction mixture was poured into water (15 mL). The mixture was extracted with ether ( $3 \times 10$  mL), and the organic extracts were dried over anhydrous magnesium sulfate and concentrated. Purification by column chromatography on silica gel (hexane-ether, 50/1) gave (1*S*\*,1'*R*\*)-1-(1'-isobutyl-2'-cyclohexenyl)nonan-1-ol in 70% yield (0.20 g). IR (neat): 3475, 3015, 2954, 2926, 2856, 1465, 1380, 1057, 980  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  0.81–0.97 (m, 9H), 1.10–1.80 (m, 22H), 1.92–2.02 (m, 2H), 3.41 (d,  $J = 8.9$  Hz, 1H), 5.46 (d,  $J = 10.3$  Hz, 1H), 5.92 (dt,  $J = 10.2, 3.8$  Hz, 1H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  14.1, 19.1, 22.7, 24.1, 24.9, 25.0, 25.5, 27.3, 27.8, 29.3, 29.7, 29.8, 30.4, 31.9, 42.8, 45.8, 76.8, 130.3, 133.1.





6.1.1.11. *4,4,5-Trimethyl-1-phenyl-5-hexen-3-ol (Generation of an Allylic Chromium Reagent from a 1,3-Diene and Addition to an Aldehyde)* (90)

To a mixture of chromium(II) chloride (0.49 g, 4.0 mmol) and vitamin B<sub>12</sub> (0.13 g, 0.10 mmol) in dry DMF (3 mL) was added a solution of 3-phenylpropanal (0.13 g, 1.0 mmol) and 2,3-dimethyl-1,3-butadiene (0.16 g, 2.0 mmol) in DMF (2 mL). The deep green mixture gradually darkened. The mixture was heated to 40°, and a DMF solution of water (0.2 M, 5 mL, 1.0 mmol) was added over a period of 2 hours. The resulting mixture was poured into water (10 mL) and extracted with ether (3 × 10 mL). The organic extracts were dried over anhydrous magnesium sulfate and concentrated. Purification of the crude product by column chromatography on silica gel gave the title product (0.20 g, 90%). Bp 98° (bath temp, 0.40 Torr); IR (neat) 3474, 3087, 3063, 3027, 2968, 1635, 1604, 1496, 1454, 1377, 1262, 1067, 1045, 894, 748, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.00 (s, 3H), 1.05 (s, 3H), 1.55–1.65 (m, 2H), 1.70 (s, 3H), 1.75–1.85 (m, 1H), 2.60–2.68 (m, 1H), 2.88–2.98 (m, 1H), 3.51 (d, *J* = 10.3 Hz, 1H), 4.84 (d, *J* = 0.6 Hz, 1H), 4.94 (t, *J* = 1.4 Hz, 1H), 7.177.32 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 19.5, 21.8, 22.1, 33.0, 33.4, 43.6, 74.7, 111.8, 125.6, 128.2, 128.4, 142.3, 150.7.



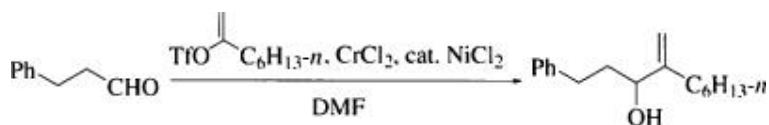
6.1.1.12. *anti-3-(2-Phenylethyl)-1-dodecene-3,4-diol (A Cross Pinacol-type Coupling Reaction between an α, β -Unsaturated Ketone and an Aldehyde)* (162)

To a mixture of chromium(II) chloride (0.98 g, 8.0 mmol) in dry, oxygen-free DMF (10 mL) was added chlorotriethylsilane (1.0 mL, 6.0 mmol), and the mixture was stirred for 30 minutes. The mixture was cooled to 0°, and a solution of nonanal (0.14 g, 1.0 mmol) and 5-phenyl-1-penten-3-one (0.32 g, 2.0 mmol) in DMF (10 mL) was added at 0°. After being stirred at 0° for 5 hours, the reaction mixture was poured into water (20 mL). The mixture was extracted with ether (3 x 20 mL) and the organic extracts were dried over anhydrous magnesium sulfate and concentrated. The crude mixture was diluted with THF (10 mL) and treated with a THF solution of tetrabutylammonium fluoride (1.0 M, 4.0 mL) at 25° for 10 minutes, and then poured into water (5 mL). The mixture was extracted with ether (3 x 20 mL), and the organic extracts were dried over anhydrous magnesium sulfate and concentrated. Purification of the crude product by column chromatography on silica gel (hexane-ethyl acetate, 50:1) gave the 3-(2-phenylethyl)-1-dodecene-3,4-diols in 99% yield (0.99 mmol, anti:syn = 93:7). Anti isomer: IR (nujol) 3442, 3026, 2925, 2855, 1497, 1456,

1377, 1074, 1000, 925, 734, 699, 666  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  0.87 (t,  $J = 6.9$  Hz, 3H), 1.20–1.35 (m, 12H), 1.54 (br, 2H), 1.72 (dt,  $J = 4.9$ , 13.0 Hz, 1H), 1.91 (br, 1H), 1.98 (dt,  $J = 5.2$ , 12.8 Hz, 1H), 2.16 (s, 1H), 2.58 (dt,  $J = 4.6$ , 12.9 Hz, 1H), 2.70 (dt,  $J = 5.5$ , 13.0 Hz, 1H), 3.44 (d,  $J = 10.4$  Hz, 1H), 5.34 (dd,  $J = 1.2$ , 10.7 Hz, 1H), 5.43 (dd,  $J = 1.2$ , 17.4 Hz, 1H), 5.90 (dd,  $J = 11.0$ , 17.4 Hz, 1H), 7.15–7.30 (m, 5H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  13.9, 22.5, 26.4, 29.1, 29.4, 29.5, 29.5, 30.2, 31.7, 36.4, 77.0, 77.7, 115.3, 125.6, 128.2, 128.2, 140.9, 142.3.

#### 6.1.1.13. *syn*-3-(2-Phenylethyl)-1-dodecene-3,4-diol

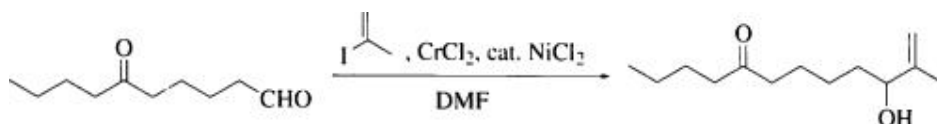
After stirring the chromium(II) chloride mixture for 30 minutes, as described above the mixture was heated at  $75^\circ$  before addition of a solution of nonanal (0.14 g, 1.0 mmol) and 5-phenyl-1-penten-3-one (0.32 g, 2.0 mmol) in DMF (10 mL). After stirring at  $75^\circ$  for 15 minutes, the reaction mixture was poured into water (20 mL). The workup was then conducted in a similar way to that for *anti*-3-(2-phenylethyl)-1-dodecene-3,4-diol above. Purification of the crude product by column chromatography gave *syn*-3-(2-phenylethyl)-1-dodecene-3,4-diol in 85% yield (0.85 mmol, *anti*:*syn* = 10:90). *Syn* isomer: IR (nujol) 3434, 3026, 2925, 2855, 1497, 1455, 1378, 1122, 1074, 998, 924, 732, 698, 666  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  0.87 (t,  $J = 6.9$  Hz, 3H), 1.20–1.35 (m, 12H), 1.56 (br, 2H), 1.83 (dt,  $J = 5.2$ , 12.8 Hz, 1H), 1.92 (dt,  $J = 5.8$ , 12.7 Hz, 1H), 2.01 (br, 1H), 2.44 (s, 1H), 2.63 (dt,  $J = 5.5$ , 13.4 Hz, 1H), 2.71 (dt,  $J = 5.5$ , 12.8 Hz, 1H), 3.45 (d,  $J = 9.2$  Hz, 1H), 5.33 (dd,  $J = 1.2$ , 10.8 Hz, 1H), 5.41 (dd,  $J = 1.2$ , 17.3 Hz, 1H), 5.85 (dd,  $J = 10.7$ , 17.4 Hz, 1H), 7.15–7.30 (m, 5H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  14.0, 22.5, 22.5, 26.5, 29.2, 29.5, 29.5, 29.5, 31.7, 39.0, 77.4, 77.7, 115.5, 125.6, 128.2, 128.2, 139.1, 142.4.



#### 6.1.1.14. 2-Hexyl-5-phenyl-1-penten-3-ol (Nickel-Catalyzed Barbier-type Addition of an Alkenylchromium Reagent to an Aldehyde) (364)

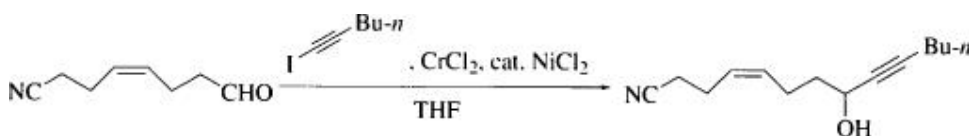
To a mixture of anhydrous chromium(II) chloride (9.8 g, 80 mmol) and anhydrous nickel(II) chloride (52 mg, 0.40 mmol) at  $0^\circ$  was added with stirring dry, oxygen-free DMF (250 mL) under an argon atmosphere. The salts dissolved in a slightly exothermic process. The mixture was stirred at  $0^\circ$  for 10 minutes. To the chromium(II) chloride-nickel(II) chloride reagent at  $25^\circ$  was added a solution of 3-phenylpropanal (2.7 g, 20 mmol) in DMF. A solution of 1-hexylethenyl triflate (10 g, 40 mmol) in DMF (60 mL) was added at  $25^\circ$  over a period of 5 minutes, then the mixture was stirred at  $25^\circ$  for 30 minutes and

monitored by TLC (ethyl acetate-hexane, 1:10). The reaction mixture was diluted with ether (200 mL), poured into ice-cold water (400 mL), and extracted with ether (3 × 100 mL). The combined extracts were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated. The crude product was distilled under reduced pressure to give 4.0–4.6 g (82–94%) of the title product. Bp 109–111°(0.11 Torr). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.2–1.4 (m, 8H), 1.72.2 (m, 5H), 2.62 (ddd, *J* = 6.6, 9.6, 13.9 Hz, 1H), 2.74 (ddd, *J* = 6.1, 9.6, 13.9 Hz, 1H), 4.10 (dd, *J* = 5.1, 7.5 Hz, 1H), 4.87 (d, *J* = 1.5 Hz, 1H), 5.04 (s, 1H), 7.1–7.4 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 14.1, 22.6, 27.9, 29.2, 31.4, 31.7, 31.9, 37.0, 74.7, 109.3, 125.7, 128.3, 128.4, 142.0, 152.0.



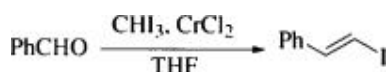
**6.1.1.15. 2-Methyl-8-oxo-1-dodecen-3-ol (Chromium-Mediated Addition of an Alkenyl Iodide to an Aldehyde under Nickel Catalysis) (9)**

A mixture of anhydrous chromium(II) chloride (1.5 g, 12 mmol) and anhydrous nickel(II) chloride (7.8 mg, 0.060 mmol) in dry, oxygen-free DMF (50 mL) was stirred at 25° for 10 minutes under an argon atmosphere. To the mixture at 25° was added slowly a solution of 6-oxododecanal (0.51 g, 3.0 mmol) and 2-iodopropene (1.0 g, 6.0 mmol) in DMF (20 mL). After being stirred at 25° for 15 minutes, the mixture was diluted with ether (50 mL), poured into water (100 mL), and the aqueous layer was extracted with ether (3 × 20 mL). The combined extracts were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated. Purification of the crude product by column chromatography on silica gel (ethyl acetate-hexane 1:2) gave 0.60 g (94%) of the title product. IR (neat) 3420, 3080, 2945, 1715, 1655, 990, 895 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.90 (t, *J* = 6.8 Hz, 3H), 1.1–1.6 (m, 10H), 1.70 (s, 3 H), 2.00 (bs, 1H), 2.30 (t, *J* = 6.8 Hz, 4H), 3.93 (t, *J* = 6.3 Hz, 1H), 4.70 (d, *J* = 1.2 Hz, 1H), 4.83 (d, *J* = 1.2 Hz, 1H).



**6.1.1.16. (Z)-8-Hydroxy-4-tetradecen-9-ynenitrile (Barbier-type Addition of an Alkynylchromium Reagent to an Aldehyde) (12)**

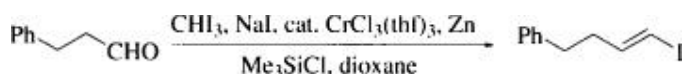
To a suspension of anhydrous chromium(II) chloride (0.50 g, 4.0 mmol) and anhydrous nickel(II) chloride (5.2 mg, 0.040 mmol) in THF (10 mL) at 25° was added slowly a mixture of (*Z*)-8-oxo-4-octenenitrile (0.14 g, 1.0 mmol) and 1-iodo-1-hexyne (0.42 g, 2.0 mmol) in THF (5 mL). After being stirred at 25° for 1 hour, the reaction mixture was diluted with ether (20 mL), poured into water (20 mL), and extracted with ether (3 × 25 mL). The combined extracts were washed with sodium chloride, dried over anhydrous sodium sulfate, and concentrated. Purification of the crude product by column chromatography on silica gel (ethyl acetate-hexane 1:2) gave 0.17 g (78%) of the product. IR (neat) 3350, 2900, 2830, 2225, 1720, 1420, 730 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.92 (t, *J* = 6.6 Hz, 3H), 1.2–1.8 (m, 6H), 2.0–2.6 (m, 9H), 4.20 (t, *J* = 6.5 Hz, 1H), 5.2–5.7 (m, 2H).



6.1.1.17. (*E*)-β -Iodostyrene [Preparation of an *E* Alkenyl Halide from an Aldehyde] (8)

To a suspension of anhydrous chromium(II) chloride (0.74 g, 6.0 mmol) in THF (10 mL) at 0° was added dropwise a solution of benzaldehyde (0.11 g, 1.0 mmol) and iodoform (0.79 g, 2.0 mmol) in THF (5 mL). After being stirred at 0° for 3 hours, the reaction mixture was poured into water (25 mL) and extracted with ether (3 × 10 mL). The combined extracts were dried over anhydrous sodium sulfate and concentrated. Purification of the crude product by column chromatography afforded 0.20 g (87%, *E*:*Z* = 94:6) of the product as a colorless oil. IR (neat): 3056, 2920, 1595, 1494, 1169, 1069, 946, 726 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 6.89 (d, *J* = 15 Hz, 1H), 7.30–7.53 (m, 5H), 7.49 (d, *J* = 15 Hz, 1H).

Low-valent chromium derived by reducing chromium(III) chloride (6.0 mmol) with lithium aluminum hydride (3.0 mmol) can be used instead of chromium(II) chloride. A combined solvent system, dioxane-tetrahydrofuran (6:1), sometimes gives better selectivity than the reaction in tetrahydrofuran with aliphatic aldehydes. (181)



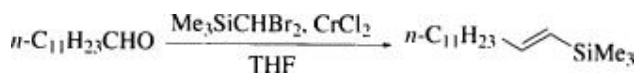
6.1.1.18. (*E*)-1-Iodo-4-phenyl-1-butene [Preparation of an *E* Alkenyl Halide from an Aldehyde - a Catalytic Version] (173)

Under an argon atmosphere, chlorotrimethylsilane (1.5 mL, 12 mmol) was added at 25° to a suspension of CrCl<sub>3</sub>(thf)<sub>3</sub> (0.15 g, 0.40 mmol), zinc (0.78 g, 12 mmol), and dried sodium iodide (0.30 g, 2.0 mmol) in dioxane (20 mL). After the mixture was stirred at 25° for 40 minutes, a solution of 3-phenylpropanal (0.27 g, 2.0 mmol) and iodoform (1.6 g, 4.0 mmol) in dioxane (20 mL) was added at 25° to the mixture over a period of 4 hours. The color of the mixture gradually turned to red during the addition. The reaction mixture was poured into water (50 mL) and the aqueous layer was extracted with hexane (3 × 30 mL). The organic extracts were washed with aqueous sodium thiosulfate and brine, dried over anhydrous magnesium sulfate and concentrated. Purification of the crude product by column chromatography on silica gel (hexane) gave 1-iodo-4-phenyl-1-butene in 84% yield (0.43 g, E:Z = 95:5) as a colorless oil together with 1-chloro-4-phenyl-1-butene (27 mg, 8%) and 4-phenyl-1-butene (5.3 mg, 2%). (*E*)-1-Iodo-4-phenyl-1-butene: IR (neat): 3061, 3026, 2924, 2855, 1604, 1496, 1453, 1025, 941, 752, 698 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.13–7.38 (m, 5H), 6.56 (dt, *J* = 14.4, 7.2 Hz, 1H(*E*)), 6.03 (dt, *J* = 14.3, 1.5 Hz, 1H), 2.72 (t, *J* = 8.1 Hz, 2H), 2.39 (q, *J* = 7.16 Hz, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 34.7, 37.8, 75.4, 126.1, 128.4, 128.4, 140.8, 145.5.



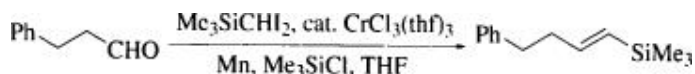
6.1.1.19. (*E*)-4-Tridecene [*E* Selective Wittig-type Olefination of an Aldehyde] (7)

To a stirred suspension of chromium(II) chloride (0.98 g, 8.0 mmol) in THF (20 mL) was added DMF (0.62 mL, 8.0 mmol) at 25° under an argon atmosphere. After being stirred for 30 minutes, a solution of nonanal (0.14 g, 1.0 mmol) and 1,1-diiodobutane (0.62 g, 2.0 mmol) (365, 366) in THF (3 mL) was added at 25°. The pale green suspension darkened, then turned into a dark brown solution. (If a lump of the chromium(II) chloride complex remained at this stage, ultrasonic irradiation was used to obtain a homogeneous solution.) The mixture was stirred at 25° for 1.5 hours, diluted with hexane (15 mL), poured into water (40 mL), and extracted with pentane (3 × 15 mL). The organic extracts were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated. Purification of the residue by short column chromatography on silica gel (hexane) afforded 0.15 g (85%, E:Z = 96:4) of the product. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.89 (t, *J* = 7 Hz, 3H), 1.2–1.5 (m, 14H), 1.9–2.1 (m, 4H), 5.3–5.5 (m, 2H).



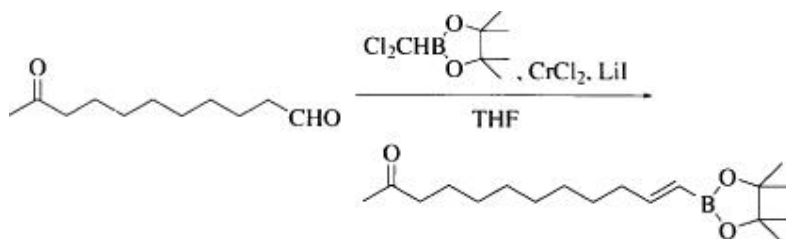
6.1.1.20. (*E*)-1-Trimethylsilyl-1-tridecene [Transformation of an Aldehyde into a Terminal *E* Alkenylsilane Using a *gem*-Dichromium Reagent] (204)

To anhydrous chromium(II) chloride (20 g, 0.16 mol) at 0° under an argon atmosphere was added dry THF (200 mL) with vigorous stirring to obtain a dispersion of chromium(II) chloride. The salt partially dissolved in a slightly exothermic process. To the suspension was added slowly at 25° a mixture of dodecanal (3.7 g, 20 mmol) and (dibromomethyl)trimethylsilane (9.8 g, 40 mmol) (207) in THF (40 mL). The mixture was stirred at 25° for 24 hours, during which it gradually turned from gray to brownish purple. The reaction mixture was poured into ice-cold water (400 mL) and extracted with hexane (3 × 100 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The crude product was purified by column chromatography on silica gel (hexane) to give 4.5 g (88%) of the product. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.01 (s, 9H), 0.84 (t, *J* = 7 Hz, 3H), 1.1–1.5 (m, 18H), 2.06 (dq, *J* = 7, 1.5 Hz, 2H), 5.58 (dt, *J* = 19, 1.5 Hz, 1H), 6.00 (dt, *J* = 19, 6.5 Hz, 1H).



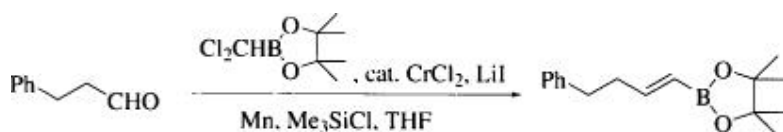
6.1.1.21. Trimethyl[(*E*)-4-Phenyl-1-butenyl]silane [Transformation of an Aldehyde into a Terminal *E* Alkenylsilane Using a *gem*-Dichromium Reagent - a Catalytic Version] (217)

Under an argon atmosphere, chlorotrimethylsilane (1.5 mL, 12 mmol) was added at 25° to a suspension of CrCl<sub>3</sub>(thf)<sub>3</sub> (0.15 g, 0.40 mmol) and manganese (0.66 g, 12 mmol) in THF (20 mL). After the mixture was stirred at 25° for 30 minutes, a solution of 3-phenylpropanal (0.27 g, 2.0 mmol) and (diiodomethyl)trimethylsilane (1.4 g, 4.0 mmol) (209) in THF (10 mL) was added at 25° to the mixture over a period of 4 hours. The reaction mixture was poured into water (50 mL) and the organic layer was extracted with hexane (3 × 30 mL). The organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated. Purification of the crude product by column chromatography on silica gel (hexane) gave the title product in 86% yield (0.36 g, *E*:*Z* = > 99:1) as a colorless oil. Bp 84° (1.0 Torr); IR (neat): 2954, 1616, 1247, 866, 838, 698 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.05 (s, 9H), 2.40 (dt, *J* = 6.3, 1.5 Hz, 2H), 2.71 (t, *J* = 7.9, 2H), 5.67 (dt, *J* = 18.6, 1.5 Hz, 1H), 6.10 (dt, *J* = 18.6, 6.0 Hz, 1H), 7.18–7.39 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ -1.2, 35.2, 38.5, 125.7, 128.2, 128.4, 130.4, 142.0, 146.1.



6.1.1.22. (*E*)-11-Oxo-1-dodecenylboronic Ester [Transformation of an Aldehyde into a Terminal *E* Alkenylboronic Ester Using a *gem*-Dichromium Reagent] (180)

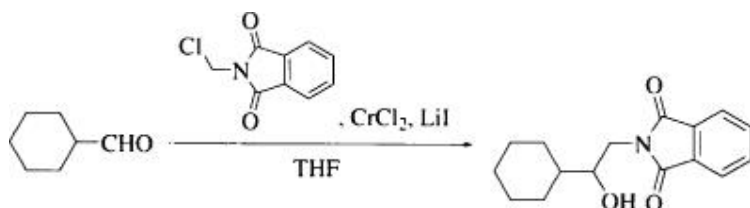
Anhydrous chromium(II) chloride (0.98 g, 8.0 mmol) was suspended in THF (10 mL) under an argon atmosphere. A solution of 10-oxoundecanal (0.18 g, 1.0 mmol) and dichloromethylboronic ester (0.42 g, 2.0 mmol) in THF (5 mL) and a THF solution of lithium iodide (0.54 g, 4.0 mmol) were successively added to the suspension at 25°. After being stirred at 25° for 4 hours, the reaction mixture was poured into water (25 mL) and extracted with ether (3 × 10 mL). The combined extracts were dried over sodium sulfate and concentrated. Purification of the crude product by column chromatography on silica gel (hexane) afforded 0.26 g (85%, *E*:*Z* = 98:2) of the product as a colorless oil. IR (neat): 2985, 2935, 2855, 1718, 1640, 1360, 1310, 1000, 975, 850 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.15–1.46 (m, 22H), 1.46–1.63 (m, 2H), 2.06–2.20 (m, 2H), 2.12 (s, 3H), 2.40 (t, *J* = 6.8 Hz, 2H), 5.40 (d, *J* = 18.0 Hz, 1H), 6.61 (dt, *J* = 18.0, 6.5 Hz, 1H).



6.1.1.23. (*E*)-4-Phenyl-1-butenylboronic Ester [Transformation of an Aldehyde into a Terminal *E* Alkenylboronic Ester Using a *gem*-Dichromium Reagent - A Catalytic Version] (217)

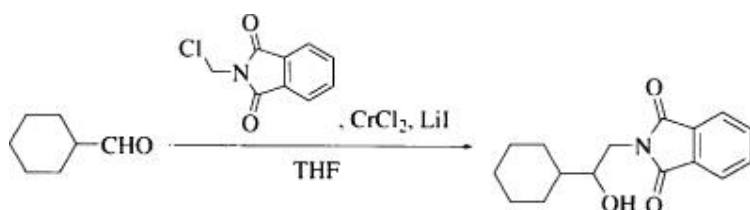
Under an argon atmosphere, chlorotrimethylsilane (0.76 mL, 6.0 mmol) was added at 25° to a suspension of CrCl<sub>3</sub>(thf)<sub>3</sub> (0.075 g, 0.20 mmol), manganese (0.33 g, 6.0 mmol), and LiI (0.54 g, 4.0 mmol) in THF (8 mL). After the mixture was stirred at 25° for 30 minutes, a solution of 3-phenylpropanal (0.13 g, 1.0 mmol) and dichloromethylboronic ester (0.42 g, 2.0 mmol) in THF (5 mL) was added at 25° over a period of 4 hours. After being stirred at 25° for a further 16 hours, the reaction mixture was poured into water (25 mL) and extracted with ether (3 × 10 mL). The combined extracts were washed with

brine (20 mL), dried over sodium sulfate, and concentrated. Purification of the crude product by column chromatography on silica gel (hexane, ethyl acetate (50:1)) afforded 0.20 g (76%, E:Z = 99:1) of title product as a colorless oil.  $^1\text{H}$  NMR(  $\text{CDCl}_3$ )  $\delta$  1.37 (s, 12H), 2.45–2.50 (m, 2H), 2.74 (t,  $J$  = 7.9 Hz, 2H), 5.56 (dt,  $J$  = 18.0, 1.5 Hz, 1H), 6.70 (dt,  $J$  = 18.0, 6.0 Hz, 1H), 7.22–7.36 (m, 5H).



**6.1.1.24. 2-(Methylthio)-1-phenyl-1-ethanol (Addition of a Sulfur-Stabilized Alkylchromium Reagent to an Aldehyde) (271)**

To a stirred suspension of chromium(II) chloride (0.49 g, 4.0 mmol) in THF (6 mL) at  $25^\circ$  under an argon atmosphere were successively added a solution of benzaldehyde (0.11 g, 1.0 mmol) in THF (2 mL), chloromethyl methyl sulfide (0.17 mL, 2.0 mmol), and a 1.0 M THF solution of lithium iodide (2.0 mL, 2.0 mmol). The mixture was stirred at  $40^\circ$  for 5 hours, poured into water (25 mL) and extracted with ether (3  $\times$  15 mL). The combined extracts were dried over anhydrous sodium sulfate and concentrated. Purification of the crude product by silica gel column chromatography (ethyl acetate-hexane, 1:5) gave 0.15 g (88%) of the product. IR (neat) 3406, 2914, 1453, 1056, 700  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (  $\text{CDCl}_3$ )  $\delta$  2.10 (s, 3H), 2.71 (dd,  $J$  = 9.0, 13.8 Hz, 1H), 2.85 (dd,  $J$  = 4.0, 13.8 Hz, 1H), 3.11 (br s, 1H), 4.75 (dd,  $J$  = 4.0, 9.0 Hz, 1H), 7.25–7.47 (m, 5H).

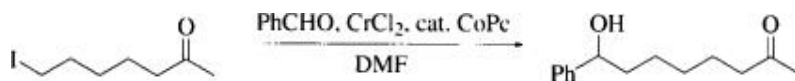


**6.1.1.25. N-(2-Cyclohexyl-2-hydroxyethyl)phthalimide (Addition of a Nitrogen-Substituted Alkylchromium Reagent to an Aldehyde) (272)**

A solution containing chromium(II) chloride (1.2 g, 10 mmol), lithium iodide (0.67 g, 5.0 mmol), cyclohexanecarboxaldehyde (0.28 g, 2.5 mmol), and N-(chloromethyl)phthalimide (1.0 g, 5.0 mmol) in THF (20 mL) was warmed

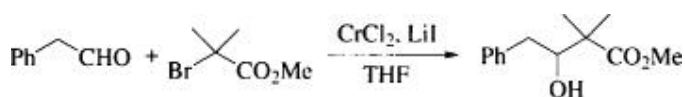


under an argon atmosphere to 55° (internal temperature). After 48 hours at 55°, the reaction mixture was worked up in the standard manner. The residue obtained after evaporation of the solvents was purified by flash chromatography (ethyl acetate-dichloromethane, 5:95), affording 0.65 g (95%) of the product. IR (KBr) 3516, 3461, 1694  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (  $\text{CDCl}_3$ )  $\delta$  1.03–1.47 (m, 6H), 1.63–2.01 (m, 6H), 3.55–3.87 (m, 3H), 7.67–7.73 (m, 2H), 7.80–7.92 (m, 2H);  $^{13}\text{C}$  NMR (  $\text{CDCl}_3$ )  $\delta$  26.0, 27.1, 27.4, 27.7, 29.1, 42.3, 42.6, 74.6, 123.4, 132.1, 134.0, 169.0.



**6.1.1.26. 8-Hydroxy-8-phenyl-2-octanone (Cobalt-Catalyzed Barbier-type Addition of an Alkylchromium Reagent to an Aldehyde) (51)**

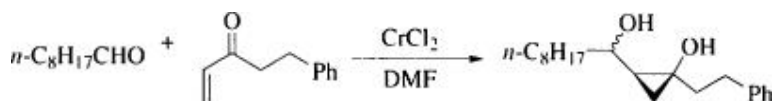
A solution of 7-iodo-2-heptanone (0.48 g, 2.0 mmol) and benzaldehyde (0.11 g, 1.0 mmol) in DMF (2 mL) was added at 30° to a stirred dark blue suspension of chromium(II) chloride (0.49 g, 4.0 mmol) and cobalt phthalocyanine (0.11 g, 0.20 mmol) in DMF (10 mL). After being stirred at 30° for 5 hours, the mixture was filtered through Hyflo-Super Cel<sup>®</sup> and the filter cake was washed with ether (10 mL). The filtrates were poured into saturated sodium chloride solution (20 mL) and the aqueous layer was extracted with ether (3 × 15 mL). The combined extracts were dried over anhydrous sodium sulfate and concentrated. Purification of the crude product by short column chromatography on silica gel (ethyl acetate-hexane, 1:3) afforded 0.20 g (89%) of the product. IR (neat) 3414, 2930, 1711, 1454, 1359, 1170, 1028, 760, 701  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (  $\text{CDCl}_3$ )  $\delta$  1.21–1.87 (m, 9H), 2.12 (s, 3H), 2.40 (t,  $J = 7$  Hz, 2H), 4.67 (t,  $J = 7$  Hz, 1H), 7.23–7.39 (m, 5H).



**6.1.1.27. Methyl 2,2-Dimethyl-3-hydroxy-4-phenylbutanoate [A Chromium(II)-Mediated Reformatsky-type Reaction] (277)**

To a suspension of chromium(II) chloride (251 mg, 2.05 mmol) and dry lithium iodide (11 mg, 0.08 mmol) in dry THF (3.2 mL) were added via syringe phenylacetaldehyde (0.086 mL, 0.738 mmol) and methyl 2-bromo-2-methylpropanoate (0.102 mL, 0.820 mmol). The resulting suspension was stirred for 1 hour at room temperature. The reaction was quenched with brine and the mixture was vigorously stirred for 15 minutes. The

organic layer was separated, and the aqueous phase was extracted three times with ether. The combined organic layers were washed with water to remove traces of chromium(III) residues, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo by rotary evaporation. The resulting organic residue was purified by flash chromatography on silica gel with 4:1 petroleum ether:ethyl acetate to afford 160 mg (98%) of the title product.  $R_f = 0.42$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.27 (s, 3 H), 1.28 (s, 3H), 2.24 (d,  $J = 5.3$  Hz, 1H), 2.54 (dd,  $J = 13.4, 10.3$  Hz, 1H), 2.81 (dd,  $J = 13.4, 2.1$  Hz, 1H), 3.69 (s, 3H), 3.92 (ddd,  $J = 10.3, 5.3, 2.1$  Hz, 1H), 7.19–7.33 (m, 5H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  20.7, 21.8, 38.4, 47.2, 52.0, 126.4, 128.5, 129.3, 129.7, 139.1, 177.7.



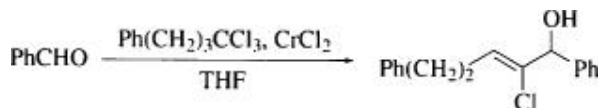
6.1.1.28. *(1R\*,2R\*)-2-(1-Hydroxynonyl)-1-(2-phenylethyl)cyclopropanols (Sequential Aldol Reaction and Cyclopropanol Formation)* (62)

To a mixture of chromium(II) chloride (0.98 g, 8.0 mmol) in dry, oxygen-free DMF (10 mL) was added a solution of nonanal (0.14 g, 1.0 mmol) and 5-phenyl-1-penten-3-one (0.32 g, 2.0 mmol) in DMF (10 mL) at  $0^\circ$ . After being stirred for 2 hours at  $0^\circ$ , the reaction mixture was poured into water (20 mL). The mixture was extracted with ether ( $4 \times 15$  mL), and the organic extracts were dried over anhydrous magnesium sulfate and concentrated. Purification of the crude product by column chromatography on silica gel (hexane-ethyl acetate, 50:1) gave the title product in 93% yield (0.28 g,  $(1'R^*):(1'S^*) = 58:42$ ).

*(1R\*,2R\*,1'R\*)-2-(1-Hydroxynonyl)-1-(2-phenylethyl)cyclopropanol*: mp  $54\text{--}58^\circ$ ; IR (nujol): 3323, 3085, 3063, 3026, 2923, 2852, 1604, 1496, 1467, 1456, 1378, 1301, 1255, 1247, 1078, 1029, 1011, 979, 904, 724,  $698\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  0.66–0.73 (m, 2H), 0.85 (ddd,  $J = 8.8, 8.7, 6.6$  Hz, 1H), 0.92 (t,  $J = 6.8$  Hz, 3H), 1.20–1.45 (m, 12H), 1.40–1.70 (m, 2H), 1.66 (dt,  $J = 7.5, 6.9$  Hz, 2H), 1.84 (ddd,  $J = 14.2, 9.3, 6.6$  Hz, 1H), 1.93 (ddd,  $J = 14.2, 9.3, 6.6$  Hz, 1H), 2.25–2.50 (br, 1H), 2.84–2.96 (m, 2H), 2.95–3.10 (br, 1H), 3.57 (dt,  $J = 8.5, 6.5$  Hz, 1H), 7.20–7.35 (m, 5H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  14.1, 17.9, 22.6, 25.8, 29.3, 29.6, 29.7, 30.0, 31.8, 32.2, 37.4, 41.2, 58.2, 73.0, 125.7, 128.3, 128.3, 142.1.

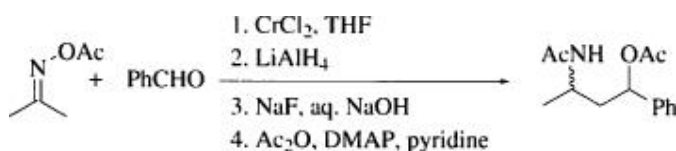
*(1R\*,2R\*,1'S\*)-2-(1-Hydroxynonyl)-1-(2-phenylethyl)cyclopropanol*: mp  $62\text{--}64^\circ$ ; IR (nujol): 3313, 3085, 3063, 3026, 2991, 2921, 2851, 1604, 1496, 1467, 1454, 1392, 1297, 1243, 1079, 1028, 1011, 953, 724,  $697\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  0.65 (dd,  $J = 9.3, 5.4$  Hz, 1H), 0.79 (ddd,  $J = 9.3, 6.0, 5.7$  Hz, 1H), 0.86 (dd,  $J = 5.9, 5.7$  Hz, 1H), 0.92 (t,  $J = 6.8$  Hz, 3H), 1.25–1.50 (m, 12H), 1.50–1.66 (m,

2H), 1.78–1.98 (m, 2H), 2.05–2.25 (br, 1H), 2.25–2.50 (br, 1H), 2.82–2.94 (m, 2H), 3.81 (dt,  $J = 6.4, 5.2$  Hz, 1H), 7.20–7.35 (m, 5H);  $^{13}\text{C}$  NMR (  $\text{CDCl}_3$ )  $\delta$  14.1, 14.9, 22.6, 25.4, 29.0, 29.3, 29.6, 29.7, 31.8, 32.1, 37.9, 41.1, 59.2, 70.0, 125.8, 128.4, 128.4, 142.0.



6.1.1.29. *(Z)*-2-Chloro-1,5-diphenyl-2-penten-1-ol (Addition of a 1-Chloro-1-alkenylchromium Reagent to an Aldehyde) (54)

A solution of 1,1,1-trichloro-4-phenylbutane (95 mg, 0.40 mmol) and benzaldehyde (42 mg, 0.40 mmol) in THF (1 mL) was added to a stirred, grayish suspension of anhydrous chromium(II) chloride (0.20 g, 1.6 mmol) in THF (10 mL) at room temperature under an argon atmosphere. After 10–12 hours, the resultant reddish reaction mixture was diluted with water, extracted three times with ether, and the combined ethereal extracts were concentrated in vacuo. Chromatographic purification of the crude product on silica gel gave 0.10 g (91%) of the *Z*-chloroalkenol. Mp 54–55°;  $R_f = 0.20$  (hexane-ether, 9:1); IR (neat): 3342, 3012, 2942, 2868, 1598, 1497, 1452, 1073, 1059, 970  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (  $\text{CDCl}_3$ , 300 MHz)  $\delta$  2.28 (d,  $J = 5.0$  Hz, 1H), 2.66–2.54 (m, 2H), 2.84–2.72 (m, 2H), 5.29 (d,  $J = 5$  Hz, 1H), 5.97 (t,  $J = 7.0$  Hz, 1H), 7.50–7.10 (m, 10H);  $^{13}\text{C}$  NMR (  $\text{CDCl}_3$ , 75 MHz)  $\delta$  29.5, 35.2, 81.1, 124.2, 125.6, 126.1, 126.5, 128.2, 129.3, 129.5, 135.1, 138.1, 141.5; MS:  $m/z$  272 ( $\text{M}^+$ ), 274 ( $\text{M}^+ + 2$ ).



6.1.1.30. 3-Acetylamino-1-acetoxy-1-phenylbutane (Preparation of a  $\gamma$ -Amino Alcohol) (68)

A mixture of chromium(II) chloride (0.66 g, 5.4 mmol) and nickel(II) chloride (70 mg, 0.54 mmol) in dry, oxygen-free THF (10 mL) was stirred at 25° for 30 minutes. A solution of benzaldehyde (0.11 g, 1.0 mmol) in THF (2 mL) and a solution of *O*-acetyl acetone oxime (0.21 g, 1.8 mmol) in THF (2 mL) was added to the suspension successively. The resulting mixture was stirred at 25° for 24 hours. The mixture was cooled to –78°, and a solution of lithium aluminum hydride in THF (1.0 M, 15 mL, 15 mmol) was added slowly to the

mixture. The resulting mixture was warmed to 0° over 2 hours and stirred at 0° for 30 minutes. Sodium fluoride (10 g), dichloromethane (18 mL), and an aqueous solution of sodium hydroxide (1.0 M, 4.4 mL) were added successively to the mixture. After being warmed to 25°, the mixture was filtered, the filter cake was washed with ethyl acetate, and the combined filtrates were dried over anhydrous magnesium sulfate. The solvent was removed and the crude product was acetylated with acetic anhydride (0.88 mL, 9.3 mmol), pyridine (0.24 mL, 3.2 mmol), and DMAP (9.8 mg, 0.080 mmol) in dichloromethane (3.5 mL). After acetylation, all volatile materials were removed under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate) to give 3-acetylamino-1-acetoxy-1-phenylbutane in 86% yield (0.22 g, 0.86 mmol, syn:anti = 70:30) as a colorless oil: *syn*-3-Acetylamino-1-acetoxy-1-phenylbutane:  $^1\text{H NMR}$  (  $\text{CDCl}_3$ )  $\delta$  1.14 (d,  $J = 6.3$  Hz, 3H), 1.82–2.15 (m, 2H), 1.93 (s, 3H), 2.08 (s, 3H), 3.94–4.03 (m, 1H), 5.38–5.44 (br, 1H), 5.73–5.78 (m, 1H), 7.27–7.37 (m, 5H). *anti*-3-Acetylamino-1-acetoxy-1-phenylbutane:  $^1\text{H NMR}$  (  $\text{CDCl}_3$ )  $\delta$  1.18 (d,  $J = 6.7$  Hz, 3H), 1.82–2.15 (m, 2H), 1.90 (s, 3H), 2.07 (s, 3H), 4.10–4.16 (m, 1H), 5.18–5.38 (br, 1H), 5.73–5.78 (m, 1H), 7.27–7.37 (m, 5H).

## 7. Tabular Survey

The literature has been reviewed up to October 2001, but several papers that have appeared in late 2001 are included.

Tables 1–13 are organized according to the sequence used in the [Scope and Limitations](#) section. Entries in Tables 1–13 are ordered by increasing carbon count of the carbonyl compound. Protecting groups are included in the carbon count. Unspecified yields are denoted by (–).

**Table 1. Reactions of Allylic Chromium Reagents with Carbonyl Compounds**

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**Table 2. Diastereoselective Addition of  $\beta$ -Substituted Allylchromium Reagents to Carbonyl Compounds**

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**Table 3. Intramolecular Coupling of Allylic (or Benzylic) Halides and Carbonyl Groups**

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**Table 4. Reactions of Heterosubstituted Allylchromiums with Carbonyl Compounds**

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**Table 5. Reactions between Propargylic Chromium Reagents and Carbonyl Compounds**

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**Table 6. Formation of Alkenyl Halides using Haloform and Low-Valent Chromium**

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**Table 7. Preparation of Olefins using 1,1-Dihaloalkanes and Chromium(II) Chloride**

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**Table 8. Preparation of Heterosubstituted Olefins with Gem-Dichromium Reagents**

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**Table 9. Reactions between Alkenyl and Aryl Halides (or Triflates) and Carbonyl Compounds**

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**Table 10. Intramolecular Coupling of Alkenyl and Aryl Halides with Carbonyl Groups**

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**Table 11. Reactions between Alkynyl Halides and Carbonyl Compounds**

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[View PDF](#)

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**Table 12. Addition of Sulfur- and Nitrogen-Substituted Alkylchromiums to Carbonyl Compounds**

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**Table 13. Reactions of Alkylchromium Reagents with Carbonyl Compounds**

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[View PDF](#)

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The following abbreviations are used in the tables:

Ac	acetyl
acac	acetylacetonate
Alloc	allyloxycarbonyl

Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bz	benzoyl
B <sub>12</sub>	cyanocobalamin (vitamin B <sub>12</sub> )
cat	catalytic amount
Cbz	benzyloxycarbonyl
cod	cyclooctadiene
CoPc	cobalt phthalocyanine
C <sub>6</sub> H <sub>11</sub>	cyclohexyl
C <sub>10</sub> H <sub>7</sub>	naphthyl
DIBAL-H	diisobutylaluminum hydride
DMA	<i>N,N</i> -dimethylacetamide
DMF	<i>N,N</i> -dimethylformamide
DMPU	<i>N,N</i> -dimethylpropyleneurea
DMSO	dimethylsulfoxide
dppe	1,2-diphenylphosphinoethane
EDTA	ethylenediaminetetraacetic acid
en	ethylene diamine
Fmoc	9-fluorenylmethoxycarbonyl
HMPA	hexamethylphosphoric triamide
MEM	(2-methoxyethoxy)methyl
MMTr	<i>p</i> -methoxyphenyldiphenylmethyl
MOM	methoxymethyl
Ms	methanesulfonyl
MS4A	molecular sieves 4Å
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NMP	1-methyl-2-pyrrolidinone
PCC	pyridinium chlorochromate
PMB	<i>p</i> -methoxybenzyl
4-PPNO	4-(3-phenylpropyl)pyridine <i>N</i> -oxide
Pro	proline
Pv	<i>tert</i> -butylcarbonyl (pivaloyl)
rt	room temperature
salen-Bu- <i>t</i>	Eq. 53
SEM	2-(trimethylsilyl)ethoxymethyl
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl



TDAE	tetrakis(dimethylamino)ethylene
TDS	hexyldimethylsilyl
TEEDA	N,N,N',N'-tetraethylethylenediamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF, thf	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMU	1,1,3,3-tetramethylurea
TMS	trimethylsilyl
Tr	triphenylmethyl (trityl)
Ts	<i>p</i> -toluenesulfonyl
Val	valine
xs	excess amount

## 8. Acknowledgments

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I would like to dedicate this chapter to Professor Hitosi Nozaki of the Japan Academy who introduced me to the exciting world of organochromium chemistry.

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# Additions of Allyl, Allenyl, and Propargylstannanes to Aldehydes and Imines

Benjamin W. Gung, Miami University, Oxford, Ohio

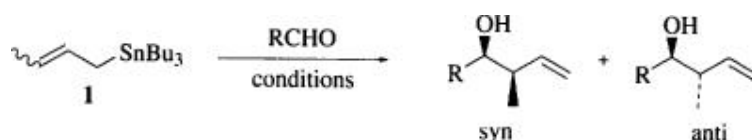
## 1. Introduction

Natural products that contain contiguous stereocenters such as those having polyacetate and polypropionate structures are of considerable interest. Current technology for constructing these chiral molecules consists of strategies broadly defined as “acyclic stereocontrol.” The most efficient tools in acyclic stereocontrol include modern aldol reactions (1-3) and the reactions of carbonyl compounds with allylmetal reagents. (4-9) In order to achieve highly efficient syntheses of natural products rich with stereochemistry, highly stereoselective transformations are required. One solution to this challenge has been the use of allylstannane reagents. Reasons that allylstannane reagents have attracted widespread interest include, but are not limited to, their ease of handling, their relative stability, and their selective reactivity. The addition of allylstannanes to aldehydes combines the process of C - C bond formation with the stereoselective production of one or two new stereocenters. The configuration of these new stereocenters is predictable on the basis of reaction conditions. Oxygen substitution at either the  $\alpha$  - or  $\gamma$  -position of allylstannanes also contributes to the versatility of these reagents. Recently developed chiral allenylstannane reagents and the use of  $\text{InCl}_3$  as a transmetalation agent have greatly enhanced the practical utilities of these reagents. Previous reviews concerning allylstannane chemistry are available, (5-9) and this review is limited mainly to carbonyl and imine addition reactions, most of which create one or two new stereocenters.

Only a few examples of addition to ketones by allylstannane reagents have been reported. These are listed in the Tables, but are not discussed in the text.

## 2. Mechanism and Stereochemistry

Three types of conditions have been developed for the addition of allylstannanes to aldehydes. These include thermal additions, additions in the presence of a Lewis acid, and additions involving prior transmetalation. The study of thermal reactions of allylstannanes began 30 years ago, (10) and Lewis acid promoted reactions became more dominant in the field about 20 years ago. (11) However, transmetalation of allylstannanes prior to their reaction with aldehydes has become the new focal point of research in recent years. (12, 13) The configuration of the products will vary depending on the reaction conditions

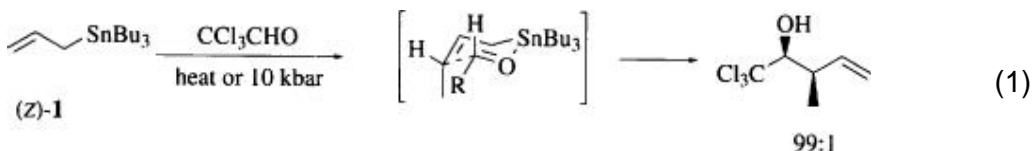


When 2-butenyl(tributyl)stannane (1) is added to an aldehyde, two new stereocenters are generated simultaneously. There are two fundamental control elements for this reaction that determine the stereochemical outcome: reagent control and substrate control. Only simple diastereoselectivity needs to be considered with achiral aldehydes, and the products are commonly denoted as syn and anti isomers. However with chiral aldehydes there are two stereochemical relationships that result in the products. Furthermore, with enantiopure aldehydes, the absolute configuration needs to be considered. In reactions under substrate control, a chiral aldehyde and an achiral stannane are employed, and the diastereoselectivity is usually based on the Felkin-Anh transition state model. (14-16) In this review, the Evans model for 1,3-asymmetric induction is also introduced to explain the observed stereochemistry with  $\beta$ -branched aldehydes. (17)

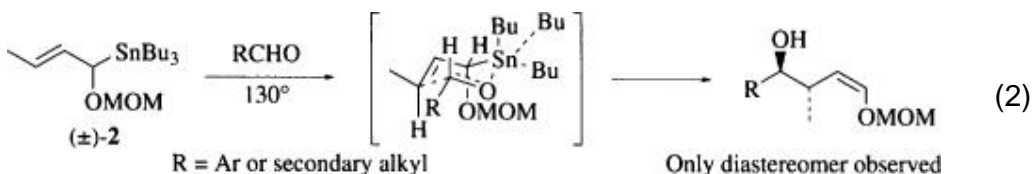
### 2.1. Thermal Additions

Reactions in the absence of a Lewis acid usually require high temperature, high pressure, or an extremely reactive aldehyde. Under these conditions, the tin atom of the stannane reagent serves as an electrophilic center associating with the carbonyl oxygen of the aldehyde. The thermal reactions are consistent with the involvement of a cyclic, six-membered, chair-like transition structure. Thus, (*Z*)- and (*E*)-2-butenyl(tributyl)stannanes react with aldehydes with good stereoselectivity to give the syn and anti homoallylic alcohols, respectively. The reaction of (*Z*)-1 with trichloroacetaldehyde is illustrative (Eq. 1). (10) The

same stereoselectivity is observed for reactions performed at room temperature but under high pressure. (18)

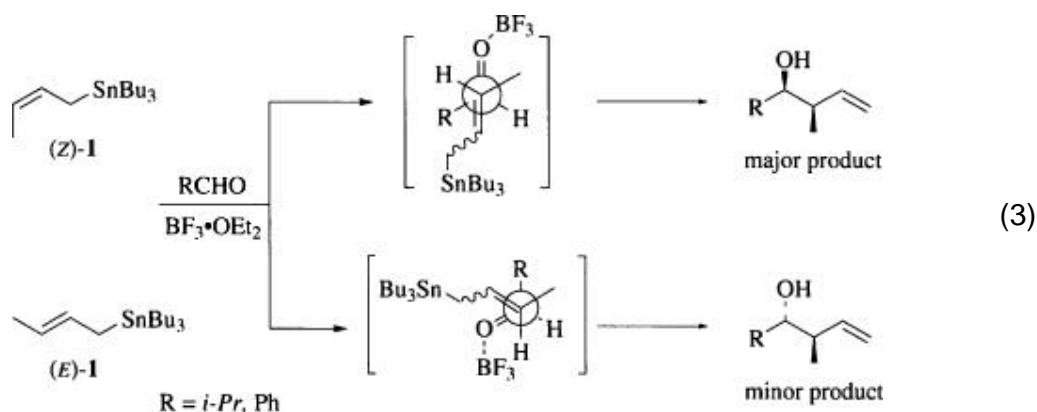


A cyclic transition structure is also believed to be involved in the thermal reactions of  $\alpha$ -alkoxy-2-butenylstannane **2** with aldehydes. (19, 20) Excellent diastereoselectivity is observed when **2** is heated with aromatic and secondary aliphatic aldehydes at 130° to give the 1,2-anti Z alkenes (Eq. 2). The configuration of the products is consistent with the participation of a six-membered, cyclic transition structure, in which the alkoxy group  $\alpha$  to tin is in an axial position. It has been suggested that the preference of the alkoxy group for the axial position may be due to a combination of steric and electronic effects. (21) Despite the excellent diastereoselectivity observed in these thermal reactions, the high temperature required for the addition often leads to low chemical yields. As a result, thermal reactions of allylstannanes have not found widespread applications.



## 2.2. Lewis Acid Promoted Additions

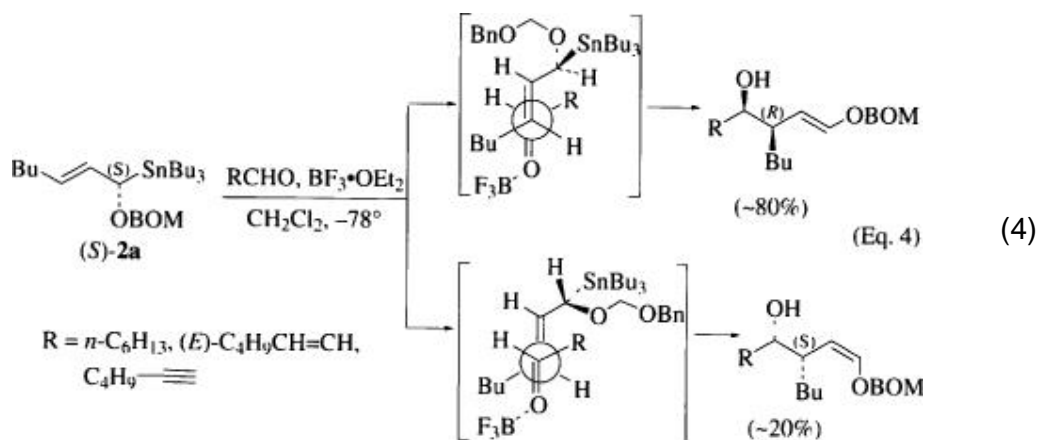
Yamamoto first reported the Lewis acid promoted addition of crotyl tributylstannanes (*E*- and (*Z*)-**1** to aldehydes in 1980. (5, 11) The  $\text{BF}_3 \cdot \text{OEt}_2$  promoted additions of **1** to benzaldehyde afford >90% of the syn homoallylic alcohol regardless of the geometry of the 2-butenyl unit. More recent studies have shown that aromatic aldehydes are less sensitive to the geometry of the 2-butenyl unit while aliphatic aldehydes, such as cyclohexanecarboxaldehyde, give variable syn/anti ratios of addition products proportional to the starting material geometry. (22) In any case, the syn isomer is always the predominant product (Eq. 3).



An acyclic transition structure was proposed, in which the boron trifluoride is coordinated to the carbonyl oxygen to activate the carbonyl group. Therefore, association of the tin center with the carbonyl oxygen is precluded, unlike as in thermal additions. Since there is no participation of a six-membered, cyclic transition structure, the geometry of the 2-butenyl unit is not of primary importance in the outcome of the product configuration. Among the possible acyclic transition structures, one antiperiplanar arrangement is suggested to lead to the syn homoallylic alcohol. (23) Steric effects are proposed to account for the preference for the syn isomer. The arrangement leading to the syn isomer has the aldehyde alkyl group anti to the methyl group of the 2-butenyl unit in the transition structure (Eq. 3), while the other arrangement, which leads to the anti isomer, has the aldehyde R group gauche to the methyl group. Torsional strain between these two alkyl groups is believed to play a significant role in determining the stereochemical outcome of the reactions. More recent studies, however, suggest that a syn synclinal arrangement is more likely to be the preferred transition state structure on the basis of both steric and secondary orbital interactions. (22)

The reactions of enantioenriched  $\alpha$ -alkoxy-2-butenyl(tributyl)stannane **2a** with aldehydes are believed to proceed by a similar mechanism (Eq. 4). (24) Lewis acid promoted additions afford mainly syn products. A molar equivalent of Lewis acid is generally required. There is a strong correlation between the stannane configuration at the allylic center and the configuration of the products. These results are consistent with the acyclic transition structure proposed for 2-butenyltrialkylstannane **1**. The major adducts are believed to be produced by way of the antiperiplanar orientation of the C = C double bond and the aldehyde C = O to minimize steric interactions between the butyl group of the stannane and the aldehyde R group. The energy difference between the two antiperiplanar transition structures has been attributed to the steric environment of the alkoxy group.



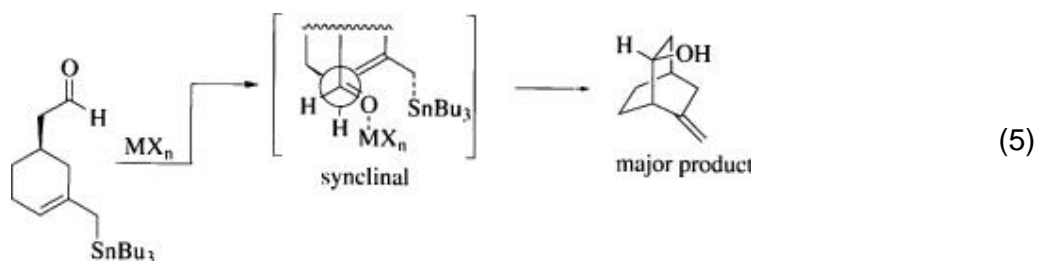


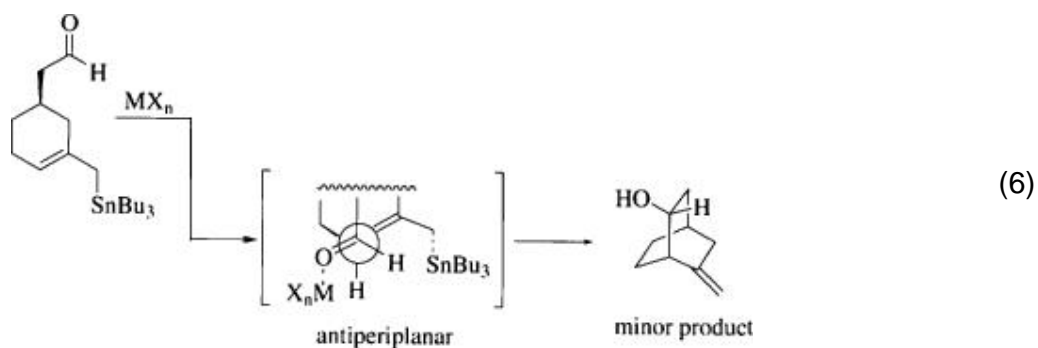
A necessary feature of this acyclic transition structure is the anti relationship between the  $\text{Bu}_3\text{Sn}$  moiety and the forming C - C bond. (6) It is this feature that accounts for the stereoselectivity observed in these additions.

Advantages of these Lewis acid promoted reactions include mild conditions and high chemical yields, while disadvantages include the low diastereoselectivity of the reagents and the difficulty in the preparations of the chiral  $\alpha$  -(alkoxy)allylstannanes.

### 2.3. Antiperiplanar vs. Synclinal Arrangement

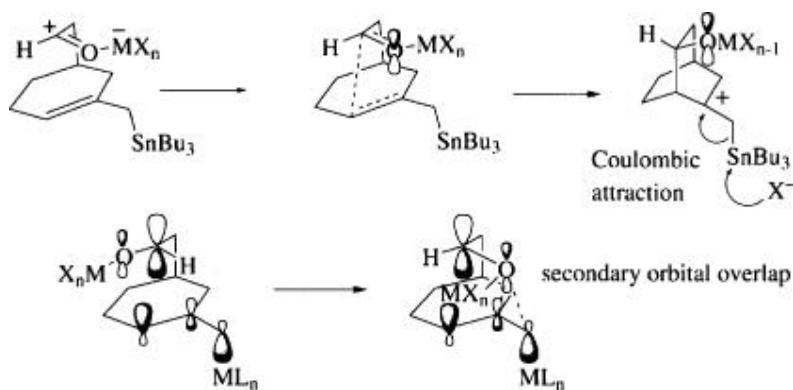
A model system designed to evaluate the relative importance of the synclinal vs. antiperiplanar arrangements in the Lewis acid promoted additions of allylstannanes to aldehydes has been reported (Eqs. 5 and 6). (25, 26)





The stereoselectivity observed for this model system suggests a preference for the synclinal orientation of double bonds. The preference for the synclinal arrangement is explained in terms of stereoelectronic effects such as secondary orbital overlap and/or minimization of charge separation in the transition structures (Figure 1).

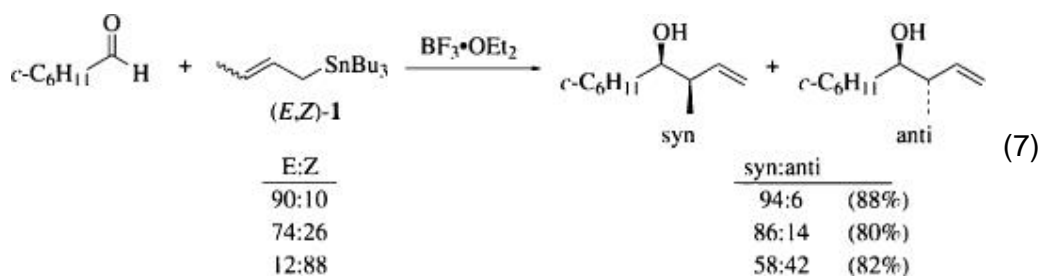
**Figure 1.** Coulombic attraction and interaction between the HOMO of the allyl metal and LUMO of the aldehyde.



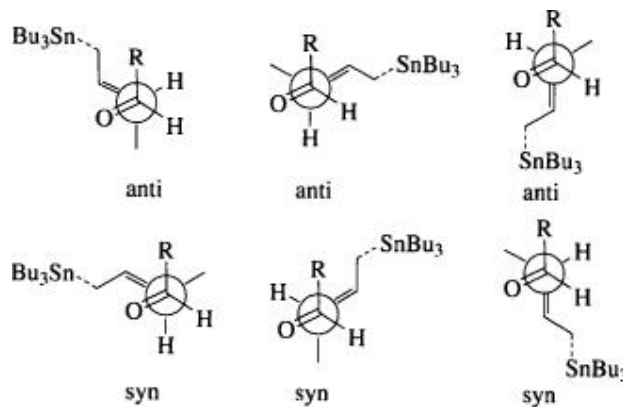
The HOMO of the allylstannane moiety and the LUMO of the aldehyde may participate in secondary orbital overlap in the synclinal transition structure. The preference for the synclinal arrangement is also explained by the minimal charge separation in this rotamer, compared to the antiperiplanar arrangement. Under otherwise identical conditions, the synclinal transition structure appears to be more favorable than the antiperiplanar arrangement. However, the steric repulsion suggested in intermolecular reactions is absent in the model system since there is a carbon tether connecting the aldehyde function and the allylstannane moiety.

The relative importance of the synclinal vs. antiperiplanar arrangements is also a consideration in  $\text{BF}_3 \cdot \text{OEt}_2$  promoted intermolecular additions of

2-butenylstannane **1** to aldehydes (Eq. 7). (22, 27) Stannane (*E*)-**1** is more selective for the formation of the syn homoallylic alcohols than (*Z*)-**1** in the case of cyclohexanecarboxaldehyde.



There are six possible staggered conformations leading to the products of these addition reactions. They are labeled “anti” and “syn” for whether they lead to anti or syn diastereomers. The energy differences among these staggered rotamers are small. The diastereoselectivity observed in the reactions of 2-butenyl(trialkyl)stannanes with aldehydes is dependent on the aldehyde structure, stannane configuration, and Lewis acid employed. (22) The higher selectivity observed for (*E*)-2-butenyl(tributyl)stannane is attributed to the synclinal arrangement (first rotamer leading to syn isomer). A similar conclusion is reached for intramolecular cyclizations in which the synclinal arrangement may be favored due to secondary molecular orbital overlap. (27)



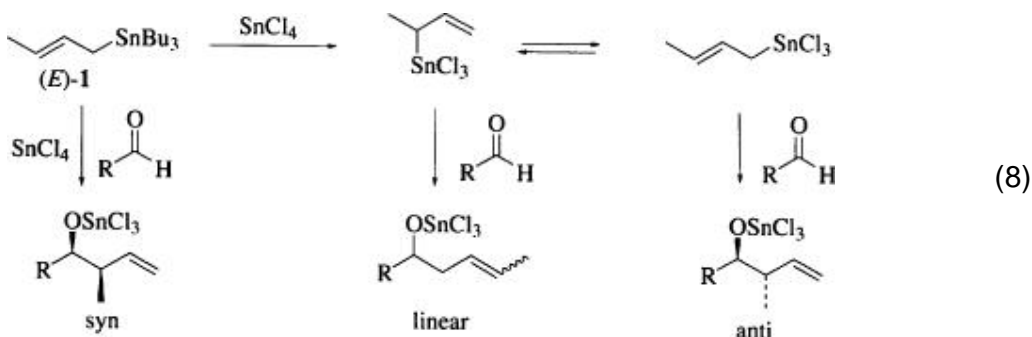
In summary, these studies conclude that there are small energy differences among the rotamers considered. The relative stabilities of the different rotamers may change as structures of the aldehydes or the stannanes change. The configuration of the products is not directly related to antiperiplanar or synclinal arrangement in the transition states in intermolecular reactions.

Continuing studies in this area are important to broaden understanding of the mechanism of stereocontrol in these reactions.

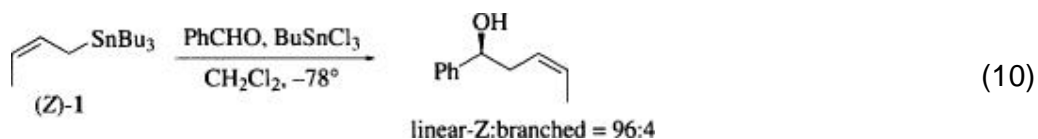
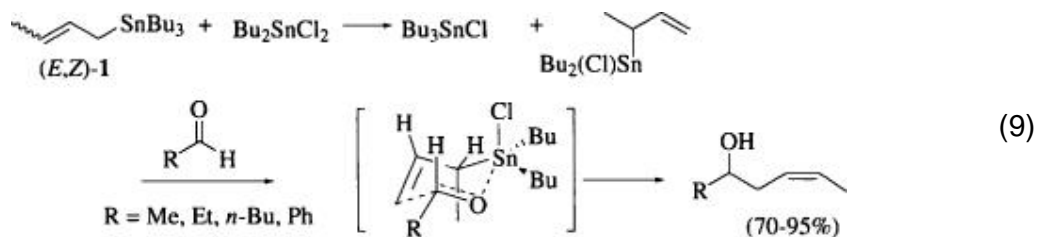
#### 2.4. Transmetalation Followed by Addition

Certain Lewis acids, such as  $\text{TiCl}_4$ ,  $\text{SnCl}_4$ , and  $\text{InCl}_3$ , react with allylstannanes in a transmetalation process. (28) The new in situ generated allylic halometal species is usually more reactive than the parent allylstannane and can react with aldehydes at low temperatures. The allylmetal reagents may undergo 1,3-migration of the metal; the rate of migration is often competitive with the addition reaction to aldehydes. This phenomenon can lead to multiple reaction pathways and complex reaction mixtures. (29, 30)

Different results may be obtained depending on the order of reagent addition, because the Lewis acid sometimes reacts with the stannane by transmetalation, producing a nucleophile that competes with the stannane itself for the aldehyde. When 2-butenyl(tributyl)stannane (**1**) is treated with  $\text{SnCl}_4$ , the species from transmetalation reacts with the aldehyde affording mainly syn and anti homoallylic alcohols. (28) This observation is consistent with participation of an  $\text{S}_{\text{E}}'$  reaction between the 2-butenylstannane and  $\text{SnCl}_4$ , generating 3-buten-2-yltin trichloride, which isomerizes to the more stable 2-butenyltin trichloride (Eq. 8).

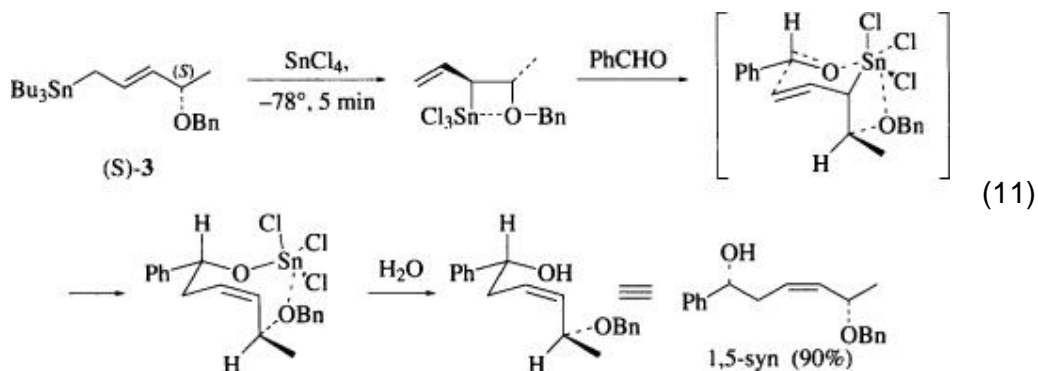


Upon addition of an aldehyde to a mixture of 2-butenyl(tributyl)stannane and  $\text{SnCl}_4$ , the syn homoallylic alcohols are produced by the usual pathway via an acyclic transition structure with  $\text{SnCl}_4$  acting as the Lewis acid. The anti homoallylic alcohols are produced by way of a six-membered, cyclic transition structure with 2-butenyltin trichloride as the actual reagent. In addition, dibutyltin dichloride and butyltin trichloride also undergo  $\text{S}_{\text{E}}'$  transmetalation reactions with 2-butenyl(tributyl)stannane (Eqs. 9 and 10). (31-36)



Depending on the character of the Lewis acid, different products can be produced through three distinct reaction pathways (Eq. 8). Adding the reagents to a mixture of the aldehyde and the Lewis acid minimizes transmetalation. Despite potential complications associated with transmetalation, more recent trends have been to employ transmetalation for control of product configuration (see below).

When chiral stannane reagent **S-3** is treated with  $\text{SnCl}_4$  at  $-78^\circ$ , the intermediate reacts with aldehydes to give a syn-1,5-enediol (Eq. 11). (12, 37) This reaction is selective for both aromatic and aliphatic aldehydes. Other products, including the 1,5-anti diastereomers, account for less than 7% of the product mixture. These reactions proceed with effective 1,5-asymmetric induction.

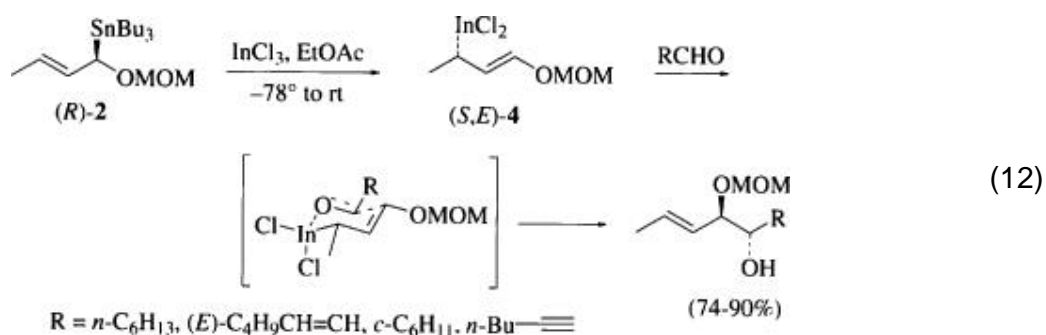


The formation of the 1,5-syn product in these reactions is consistent with a

mechanism that involves initial transmetalation of the stannane to give the allylic tin trichloride. It is believed that this trichlorostannane is stabilized by coordination of the oxygen of the benzyloxy group to the electron-deficient tin atom (Eq. 11). The coordination complex is formed stereoselectively so that the methyl and vinyl groups are trans-disposed about the four-membered ring. The allylic tin trichloride then reacts with the aldehyde, which is added 5 minutes after the allylstannane and SnCl<sub>4</sub> are mixed. A six-membered, chair-like, cyclic transition structure controls the facial selectivity of the reaction and establishes the Z geometry of the double bond in the product.

The mild Lewis acid InCl<sub>3</sub> undergoes transmetalation with α-alkoxy-2-butenyl-stannanes in various donor solvents such as ethyl acetate or acetonitrile (Eq. 12). (38). The anti:syn ratio approaches 98:2 when the reaction is performed at low temperature. These allylic indium intermediates react with aldehydes to yield anti 1,2-diol monoethers directly. Anti 1,2-diols with greater than 95% ee are obtained from an α-MOM allylic stannane of equal enantiomeric purity. A simplified pathway is presented to explain the stereospecificity (Eq. 12). The chiral stannane (*R*)-2 experiences anti S<sub>E</sub>2' attack on the InCl<sub>3</sub> to afford mainly the S,E γ-alkoxy crotyl indium species 4. Subsequent addition to the aldehyde takes place through a chair-like, cyclic transition structure affording the anti product. However, the InCl<sub>3</sub> promoted reactions of 2-butenylstannanes proceed with 2-butenylindium dichloride as the actual addition reagent. (38)

Studies in allylstannane chemistry have evolved from an emphasis on thermal reactions, (10) through Lewis acid promoted reactions, (11) to a current focus on transmetalation prior to addition to aldehydes. Current research seeks to further promote that stereochemical outcomes can be better controlled through transmetalation prior to additions. (13)

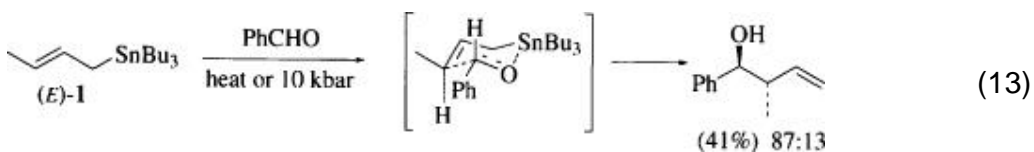


### 3. Scope and Limitations

#### 3.1. Reactions of Simple Allyl- and 2-Butenylstannane Reagents

##### 3.1.1.1. Thermal Reactions

Thermal additions of E 2-butenylstannanes to aldehydes proceed with good to excellent stereoselectivity to give anti homoallylic alcohols (Eq. 13). However, because of the high temperatures or pressure required, their use in synthesis is limited to simple aldehydes. (39)



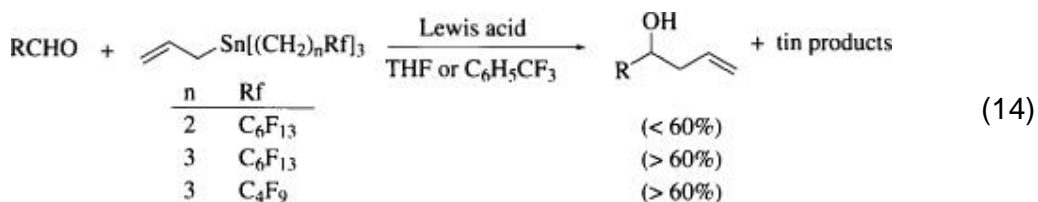
##### 3.1.1.2. Lewis Acid Promoted Reactions

###### 3.1.1.2.1. Reactions with Achiral Aldehydes

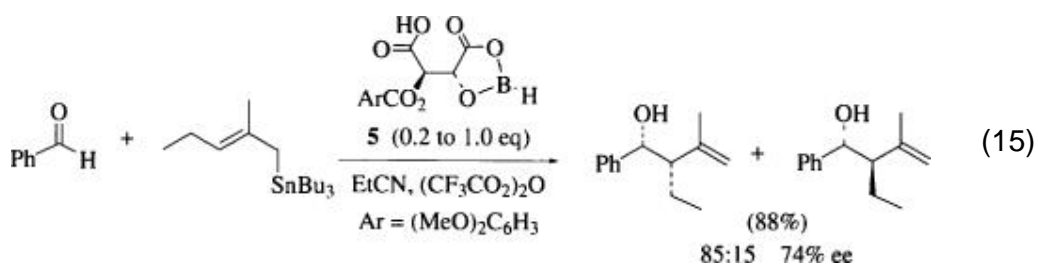
Lewis acid promoted reactions between allylstannanes and aldehydes typically proceed at  $-78^{\circ}$  and have become practical methods in organic synthesis.

Reactions between 2-butenyl(tributyl)stannane (1) and aldehydes in the presence of boron trifluoride give syn homoallylic alcohols as the major products with stereoselectivities in the range 90:10 to 98:2 irrespective of the stannane geometry (see Eq. 3). (5, 11) When other Lewis acids are examined, mixtures of isomers are observed (see "Transmetalation Followed by Addition" in this section). (28) The geometry of the 2-butenylstannane has a small influence on the configuration of the products. (22)

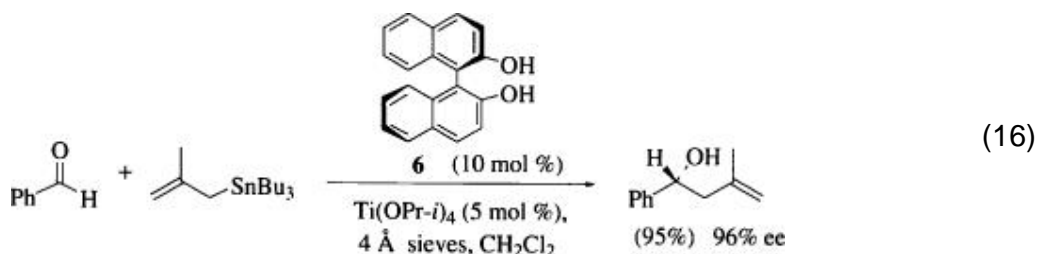
Recently, a new class of tris-(perfluoroalkylpropyl)allylstannane reagents has been reported (Eq. 14). (40-42) The reagents were developed to facilitate the separation of toxic tin byproducts in organic synthesis. The tris-(alkylpropyl)allylstannane is better than the corresponding tris-(perfluoroalkylpropyl)allylstannane because of its solubility in organic solvents. This new class of "fluorous" reagents is suitable for Lewis acid promoted additions to aldehydes and enables simple workup procedures. (40)



The tartrate derived chiral (acyloxy)borane catalyst (CAB, **5**) promotes catalytic enantioselective reactions of allylic stannanes with aldehydes (Eq. 15). (43) Both aliphatic and aromatic aldehydes can be employed with substituted allylstannanes to produce homoallylic alcohols in good yield and moderate to high regio- and enantioselectivities.

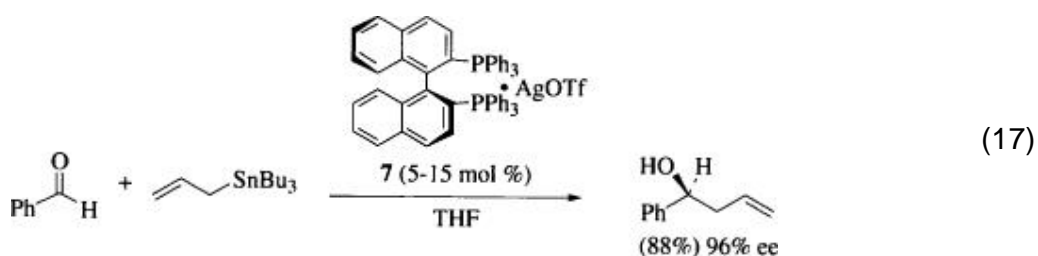


A number of binaphthol (**6**) derived chiral Lewis acids have also been applied to the addition of allylstannanes to aldehydes. (44-49) Initial studies used BINOL and either  $\text{Ti}(\text{OPr-}i)_4$  or  $\text{TiCl}_2(\text{OPr-}i)_2$  as the Lewis acid promoter. Good yields of homoallylic alcohols with high enantiomeric enrichment are obtained with as little as 10 mol % of the catalyst (Eq. 16). (44) The reaction rate is accelerated when  $i\text{-PrSSiMe}_3$  is added, allowing as little as 2% of the catalyst to be used. (49) The effect of  $i\text{-PrSSiMe}_3$  is presumably due to the formation of  $\text{Bu}_3\text{SnSPr-}i$  and  $\text{Me}_3\text{SiOR}$ , which results in regeneration of the catalyst.



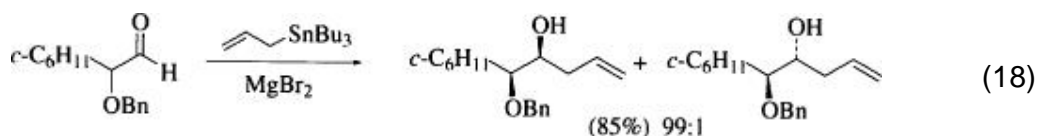
The chiral Lewis acid complex S-BINAP·AgOTf (**7**) catalyzes reactions of allylstannanes with aldehydes (Eq. 17). (50, 51) The optimal catalyst is generated from a combination of BINAP and AgOTf. This catalyst is more efficient with aromatic aldehydes than with aliphatic aldehydes as measured in both chemical yield and enantioselectivity. It is believed that the BINAP·Ag(I) complex acts as a chiral Lewis acid catalyst rather than as a transmetalation reagent.



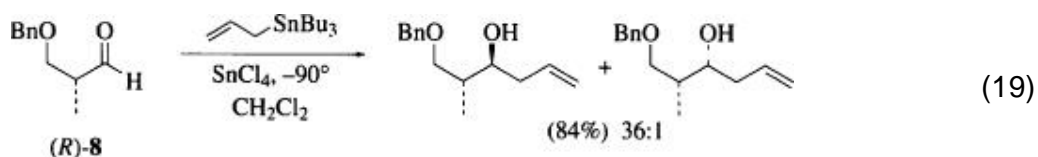


### 3.1.1.2.2. Reactions with Chiral Aldehydes

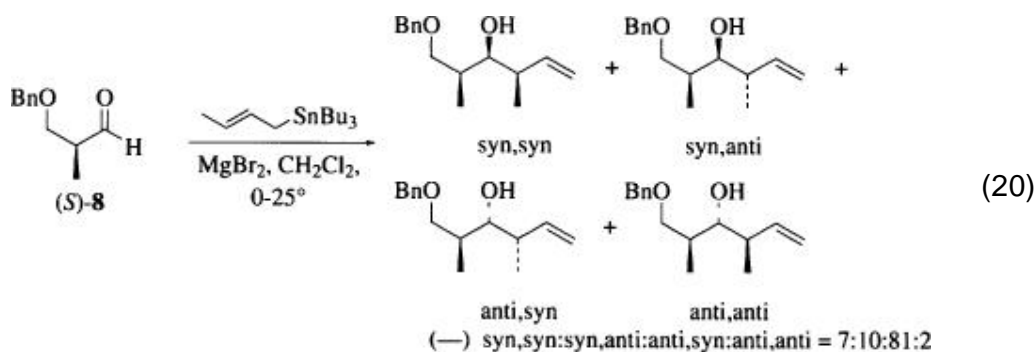
The Lewis acid promoted additions of allyltributylstannane to chiral  $\alpha$ -alkoxy aldehydes give varying degrees of diastereofacial selectivity depending on the Lewis acid and the aldehyde appendages (Eq. 18). (52) The addition of allyltributylstannane to an  $\alpha$ -benzyloxy aldehyde is highly syn-selective when  $\text{MgBr}_2$  is used as the promoter (53, 54) under Cram chelation control. (14, 55) When  $\text{BF}_3 \cdot \text{OEt}_2$  is the promoter, the addition to  $\alpha$ -*tert*-butyldimethylsilyloxy (TBDMSO) aldehydes proceeds via the Felkin-Anh model (16, 56) of facial selection to give the anti products. Boron trifluoride has only one coordination site, and therefore cannot form a chelate. The TBDMS protecting group is also known to disfavor chelate formation. (57)



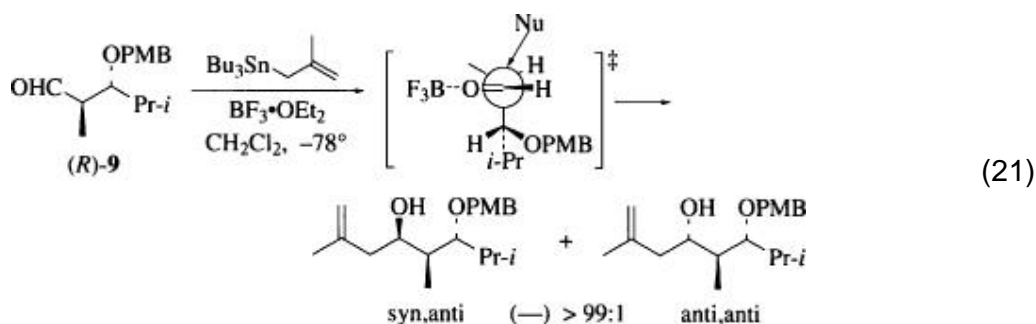
Highly anti selective additions can be realized with  $\alpha$ -methyl- $\beta$ -benzyloxy aldehyde **8** and allyltributylstannane using  $\text{SnCl}_4$  as the Lewis acid. (58-60) The reaction must be carried out at low temperatures ( $-90$  to  $-100^\circ$ ) in order to achieve high diastereofacial selectivity. At low temperatures, the six-membered chelate formed between the aldehyde and  $\text{SnCl}_4$  should be more stable, producing the Cram chelation product (Eq. 19). Competitive transmetalation apparently does not occur at  $-90^\circ$ , resulting in an acyclic transition state for the addition reaction. Thus the tin(IV) chloride serves only as Lewis acid with the aldehyde.



Diminished stereocontrol is observed in the Lewis acid promoted reactions of aldehyde **8** with 2-butenylstannane **1** (Eq. 20). (58) The chelation-controlled reaction catalyzed by  $\text{MgBr}_2$  is relatively more selective. The observed stereoselectivity is consistent with the Cram chelation-control model.



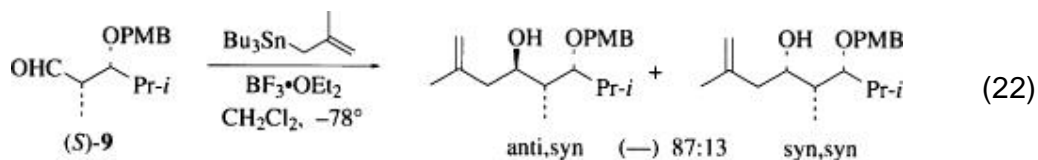
Reactions between a chiral aldehyde and an achiral nucleophile proceed under substrate control. Although aldehyde **8**, with one  $\alpha$ -stereocenter, shows only a modest diastereofacial bias, chiral aldehyde (*R*)-**9** with a second stereocenter at the  $\beta$ -carbon shows excellent stereoselectivity under similar reaction conditions (Eq. 21). (17)



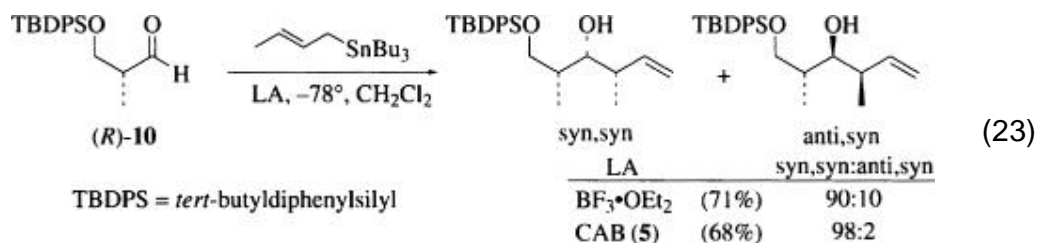
Aldehydes with two stereocenters and allyl- and methallyltributylstannanes react in the presence of boron trifluoride to give homoallylic alcohols with >99:1 stereoselectivity. The product configuration is consistent with the nucleophilic attack following the Felkin-Anh model. (17, 61) This is an example of merged 1,2- and 1,3-asymmetric induction, with the stereogenic centers operating in a cooperative fashion to direct the facial selection. (11) Although there are relatively few examples to demonstrate the generality of this trend, all reported

results follow the selection rules. The enhanced selectivity is explained as shown in Eq. 21. The relative orientation of the  $\text{BF}_3$ -complexed carbonyl and the  $\alpha$ -chiral center follow the Felkin-Anh model, resulting in a 1,2-syn, 1,3-anti stereochemical relationship.

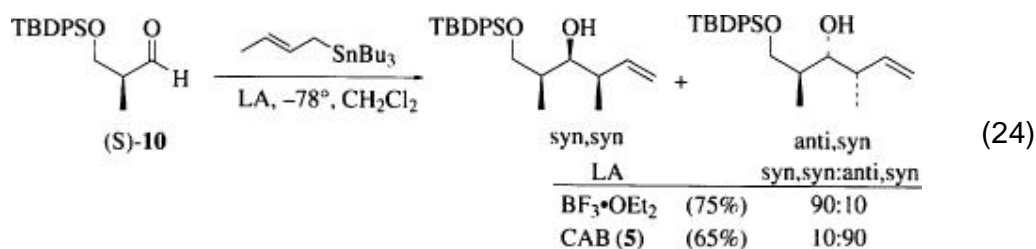
Under the same conditions the 2,3-syn aldehyde diastereomer (*S*)-**9** produces the anti, syn isomer with reduced selectivity (Eq. 22). This finding is consistent with a mismatch in 1,2- and 1,3-asymmetric induction with a higher level of control of facial selectivity by the  $\beta$ -stereocenter. When a bulky Lewis acid ( $\text{Ph}_3\text{CClO}_4$ ) is employed, the process reverts to 1,2-stereocontrol and the syn, syn product is predominant. This reversal in aldehyde facial induction indicates that the  $\alpha$ -stereocenter becomes the dominant control element as the steric demands of the Lewis acid increase. (17)



Reactions of the  $\alpha$ -methyl- $\beta$ -silyloxy aldehyde **10** with 2-butenyl(tributyl)stannane (**1**) have been studied with one equivalent of either  $\text{BF}_3 \cdot \text{OEt}_2$  or the chiral catalyst CAB (**5**) (Eqs. 23 & 24). (62) This study provides an example of a reaction with both a chiral aldehyde and a chiral promoter. A matched/mismatched pairing of the aldehyde and CAB promoter is observed. It was previously shown that CAB promotes the addition of allylic stannanes to achiral aldehydes in up to 90% ee. The dipropionate adduct with syn, syn configuration is obtained with 98:2 diastereoselectivity when CAB is used as the promoter with the aldehyde (*R*)-**10** (Eq. 23). The  $\text{BF}_3 \cdot \text{OEt}_2$  promoted reactions give 90:10 diastereofacial selectivity in favor of the syn, syn isomer with either aldehyde (Eqs. 23 and 24).

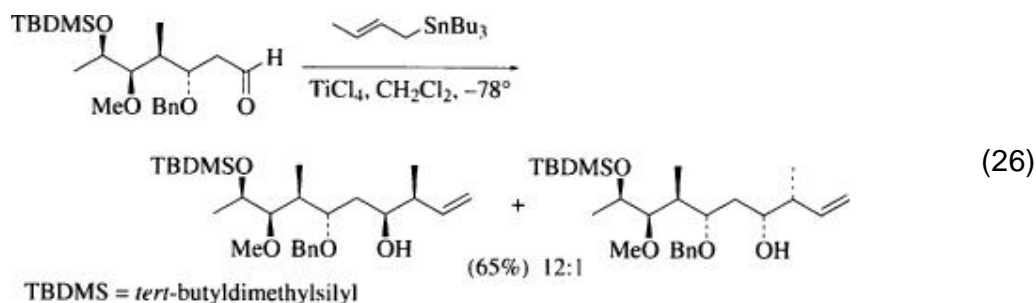
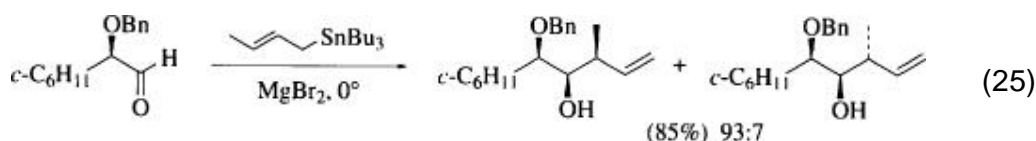


TBDPS = *tert*-butyldiphenylsilyl



The reaction promoted by CAB with the aldehyde (S)-**10** affords 90:10 diastereoselectivity in favor of the anti, syn product (Eq. 24). The chiral Lewis acid CAB overrides the diastereofacial bias of aldehyde (S)-**10** in this case. Similar to a previous example involving aldehyde **8** (Eqs. 19 and 20), the  $\alpha$ -methyl-  $\beta$ -alkoxy aldehyde **10** has a relatively weak diastereofacial bias.

MgBr<sub>2</sub> promoted additions of 2-butenyl(tributyl)stannane (**1**) to  $\alpha$ -alkoxy chiral aldehydes gives a mixture of isomers in the range of 93:7 in favor of the syn, syn diastereomer (Eq. 25). (22, 63) The starting stannane **1**, enriched in the E isomer, gives slightly higher selectivity than the stannane **1** mixture that is enriched in the Z isomer. The addition of **1** to the  $\beta$ -alkoxy aldehyde shown in Eq. 26 preferentially gives the 1,3-anti diol when either TiCl<sub>4</sub> or BF<sub>3</sub>·OEt<sub>2</sub> is used as the promoter. (64) Both the Cram chelation model and the Evans dipolar model predict the anti product.



In Lewis acid mediated additions, allylstannanes attach to aldehydes through an open transition state. Therefore, 1,2-syn configuration is obtained in the

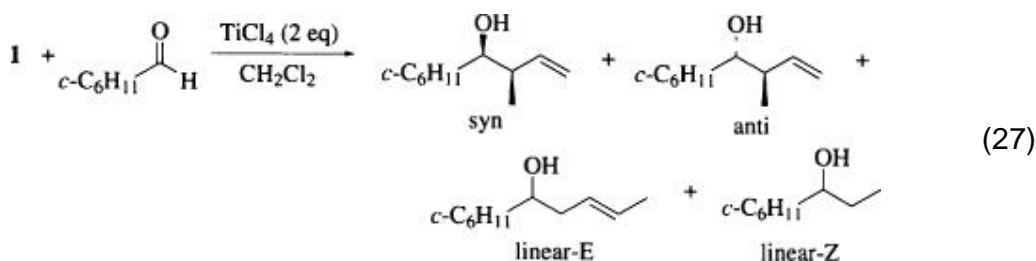
major product when 2-butenylstannane is used. As described in this section, the configuration of the substrate controls the stereochemistry of the product in a predictable course, i.e., 1,2-syn and 1,3-anti product configurations are favored. The diastereoselectivity varies depending on the substrates and reaction conditions. The ready availability of various allylstannanes from their corresponding 2-alkenyl halides and the predictability of the stereochemical outcome have made allylstannane reagents a popular choice for many synthetic chemists.

### 3.1.1.3. Transmetalation Followed by Addition

Certain Lewis acids (either achiral or chiral) react with allylstannanes to give new allylmetal species, which afford homoallylic alcohols in a stereocontrolled fashion when reacted with aldehydes. The desired outcome can be obtained by choosing an appropriate Lewis acid.

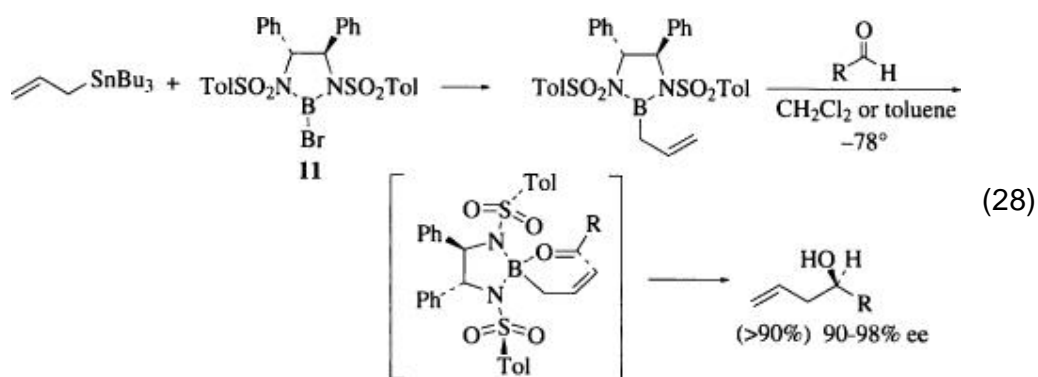
### 3.1.1.4. Reactions Promoted by $TiCl_4$

Transmetalation occurs when  $TiCl_4$  is used as the Lewis acid. A crossover in syn/anti preference is observed when the order of addition of the reactants is reversed. Addition of the 2-butenylstannane **1** to a 1:1 mixture of the aldehyde and  $TiCl_4$  affords the syn adduct as the major product (Eq. 27). However, when the aldehyde is added to premixed stannane and excess  $TiCl_4$  the anti isomer is predominant. It is proposed that a transient allyltitanium species is generated, which adds to the aldehyde through a cyclic transition structure. (28) When the Lewis acids employed are  $SnCl_4$ ,  $BuSnCl_3$ , or  $Bu_2SnCl_2$ , transmetalation also occurs prior to aldehyde addition (Eqs. 10 & 11). The major product is usually the linear Z alkene. (31-36)

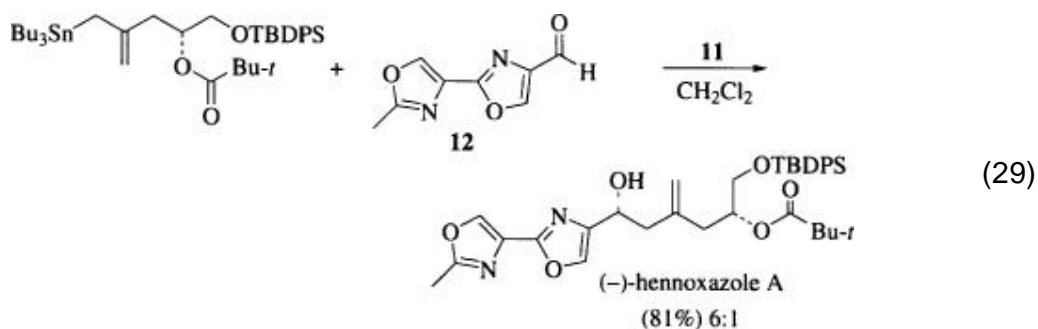


#### 3.1.1.4.1. Reactions Promoted by a Chiral Borane

The (*R,R*)- and (*S,S*)-1,2-diamino-1,2-diphenylethane derived bromoborane **11** promotes enantioselective reactions of allylic stannanes with aldehydes (Eq. 28). (65) Both aliphatic and aromatic aldehydes can be employed with the allylstannane to produce homoallylic alcohols in high yield and high enantioselectivity. A chiral allylic borane species is believed to be the intermediate.

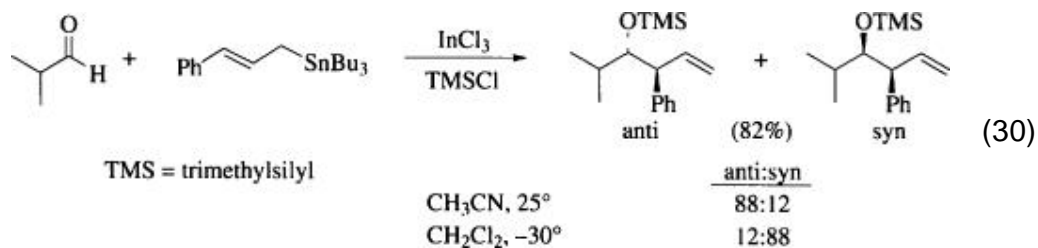


A number of applications of this methodology using more complex allylstannanes are reported. (66, 67) An example is shown for the preparation of the marine alkaloid (–)-hennoxazole A (Eq. 29). (67) The formation of the key intermediate homoallylic alcohol is achieved by transmetalation of the allylic stannane with bromoborane (*R,R*)-**11** to yield an allylic borane for addition to aldehyde **12**. Stereocontrol is principally induced from the sulfonamide in this case.

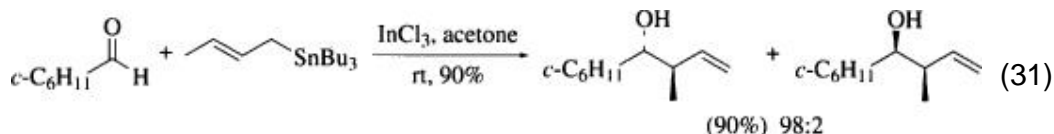


#### 3.1.1.4.2. Reactions Promoted by InCl<sub>3</sub>

Cinnamyl tributyltin adds to isobutyraldehyde in the presence of InCl<sub>3</sub>. (68) In this case, InCl<sub>3</sub> serves as the catalyst and TMSCl is used as the catalyst-liberating reagent (Eq. 30). The diastereoselectivity of the addition is solvent dependent ranging from 88:12 anti:syn in acetonitrile at 25°, to 12:88 anti:syn in methylene chloride at –30°. The former addition proceeds by transmetalation to the cinnamyl dichloroindium species, which adds to the aldehyde by way of a cyclic transition state. In the latter addition, InCl<sub>3</sub> serves as a Lewis acid and the reaction proceeds by the usual acyclic transition state to give predominantly the syn adduct.



$\text{InCl}_3$  is found to undergo transmetalation with 2-butenylstannane **1** in acetone and acetonitrile and the resulting intermediates afford anti adducts with aldehydes (Eq. 31). (38) These findings allow direct access to anti homoallylic alcohols and expand the scope of the reactions of 2-butenyl(tributyl)stannane.

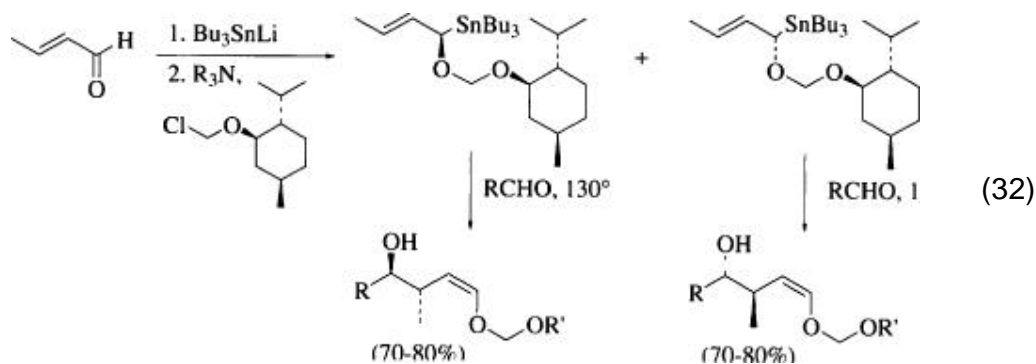


The reactive nature of allylstannanes makes it possible to transfer the allyl group to a different metal center (Ti, B, and In) before the addition to a carbonyl group occurs. This new allylmetal species can react with different stereochemical outcomes. Thus transmetalation provides a means to expand the scope of allylstannane chemistry. More work is needed in this area to explore the scope and limitations of transmetalation.

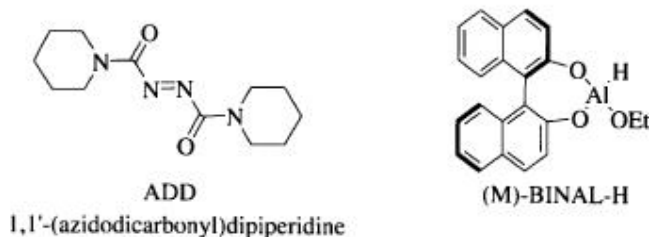
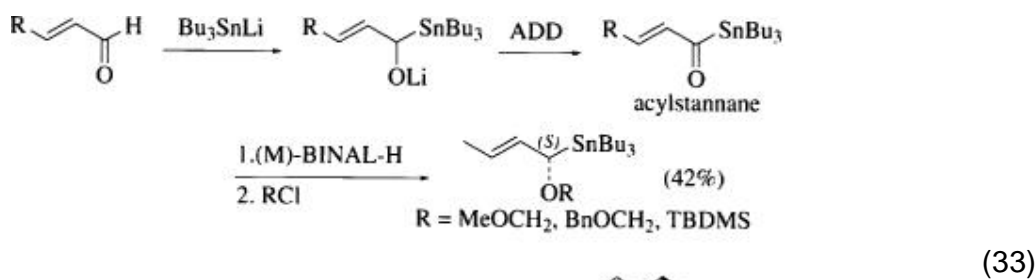
### 3.2. Reactions of $\alpha$ -(Alkoxy)allylstannane Reagents

#### 3.2.1.1. Preparation of $\alpha$ -(Alkoxy)allylstannane Reagents

Racemic  $\alpha$ -(alkoxy)allylstannane reagents are prepared by the addition of (tri-*n*-butylstannyl)lithium to (*E*)-2-butenal followed by protection of the hydroxy group with methyl chloromethyl ether (MOMCl) or benzyl chloromethyl ether (BOMCl). (69, 70) Enantiomerically pure  $\alpha$ -(alkoxy)allylstannane reagents were initially prepared by replacing the MOM ether protecting group with (-)-(menthyloxy)methyl ether followed by chromatographic separation of the resulting diastereomers (Eq. 32). (71)



A more general, but also more technically demanding, approach to enantioenriched  $\alpha$ -(alkoxy)allylstannanes involves asymmetric reduction of the stannyl ketone, which is obtained by oxidation of the  $\alpha$ -hydroxystannane (Eq. 33). (24, 72) Reduction of the acylstannane with BINAL-H reagents (73) or with the Chirald<sup>®</sup> reagent produces enantioenriched  $\alpha$ -hydroxystannanes. (“Chirald reagent” is a complex formed from LiAlH<sub>4</sub> and Darvon alcohol. Darvon alcohol is available from Aldrich Chemical Company as “Chirald<sup>®</sup> [(2*S*,3*R*)-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol].) The BINAL-H reduction affords materials of 95% ee or better. The Chirald reagent is less selective yielding alcohols of 70% ee. These hydroxystannanes are unstable and should be converted into stable alkoxyethyl or silyl ethers immediately after they are generated.



### 3.2.1.2. Thermal Reactions

Thermal additions of  $\alpha$ -(alkoxy)allylstannanes to aromatic and secondary alkyl aldehydes proceed efficiently to give the 1,2-anti *Z* alkenes with excellent

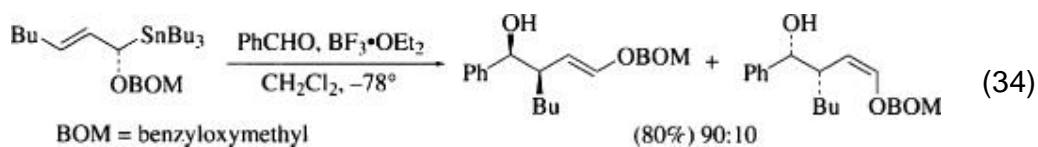


stereoselectivity (see Eq. 2). (19, 20) However, because of the high temperatures required for these reactions, thermal additions have not found widespread use in synthesis.

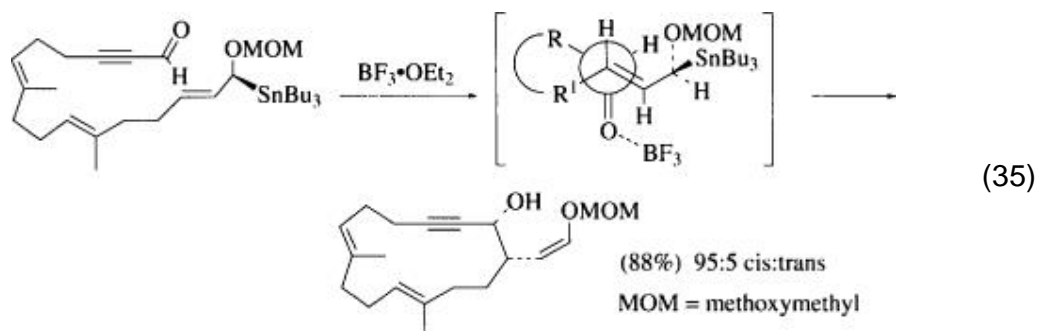
### 3.2.1.3. Lewis Acid Promoted Reactions

#### 3.2.1.3.1. Reactions with Achiral Aldehydes

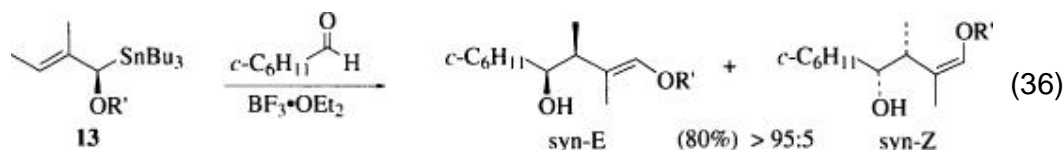
Boron trifluoride promoted reactions between enantioenriched  $\alpha$ -(alkoxy)allylstannanes and aldehydes proceed at  $-78^\circ$  through an allylic inversion process ( $S_E'$ ). (24) In contrast to thermal reactions,  $BF_3 \cdot OEt_2$  promoted reactions afford mainly syn products with syn:anti ratios in the range of 90:10 (Eq. 34). Stereoinduction from the stannane reagents to the homoallylic alcohols is high with the major product containing an E enol ether and the minor isomer a Z enol ether. These two diastereomeric products have opposite configurations at the two stereocenters.



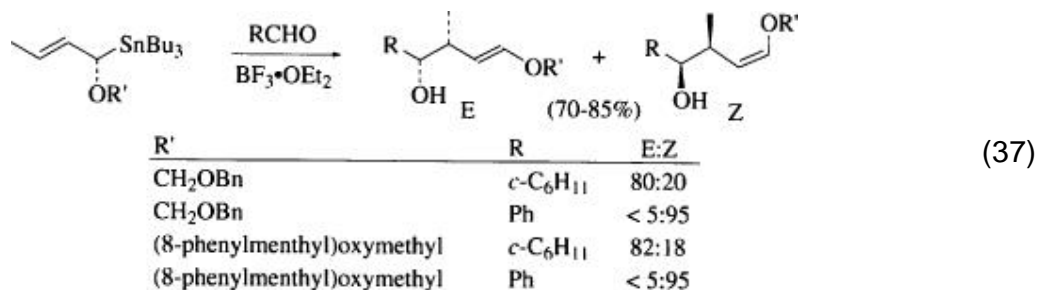
Although the intermolecular reactions of  $\alpha$ -(alkoxy)allylstannanes and aldehydes produce mainly the diastereomer with an E enol ether, the corresponding intramolecular reactions afford mainly the Z enol ether. (74) The enantioenriched S  $\alpha$ -alkoxy allylic stannanyl ynal depicted in Eq. 35 is treated with  $BF_3 \cdot OEt_2$  at  $-78^\circ$  giving the 14-membered cembranolide precursor in 88% yield with only minor amounts of other diastereomers. (74) The preference for the Z enol ether isomer is explained by assuming a synclinal transition structure. Since the aldehyde and stannane are connected by a carbon tether in the intramolecular reaction, the antiperiplanar arrangement of  $C=O$  and  $C=C$  is disfavored. The usually unfavorable steric interactions between  $R^1$  and  $R$  are overcome in the intramolecular reactions. The alternate synclinal transition state, which would produce an E enol ether, appears to be disfavored possibly due to the “outside” alkoxy arrangement. (75, 76)



The addition of  $\beta$ -methyl- $\alpha$ -(alkoxy)allylstannane **13** to aldehydes in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$  has also been studied. (77) Of the four possible diastereomeric products, a uniformly high yield of syn-E-isomer is obtained (Eq. 36). The stannane **13** fails to react with benzaldehyde under the same conditions.

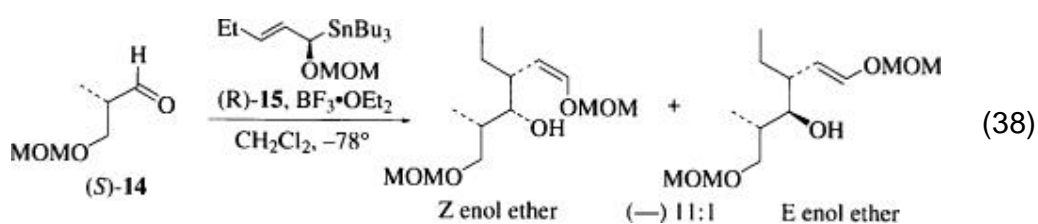


Fair to good syn E selectivities are observed for the reactions of  $\alpha$ -(alkoxy)-2-butenylstannanes with aliphatic aldehydes, while excellent syn Z selectivities are observed with aromatic aldehydes (Eq. 37). (78, 79) The difference between aromatic and aliphatic aldehydes is explained on the basis of steric and electronic effects as well as the importance of the Lewis acid-aldehyde complexes. (79-81)



#### 3.2.1.4. Reactions with Chiral Aldehydes

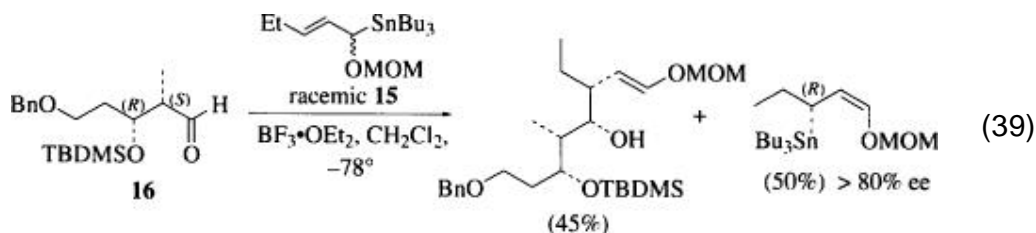
Double stereodifferentiation is observed when  $\alpha$ -(alkoxy)allylstannanes are treated with  $\alpha$ -substituted aldehydes in the presence of boron trifluoride. (82) The reaction of aldehyde (S)-14 with stannane (R)-15 proceeds at  $-78^\circ$  to give an 11:1 mixture of Z and E enol ethers in 85% yield (Eq. 38). The configuration of the major isomer is consistent with the Felkin-Anh model of facial selection with respect to the aldehyde. The syn relationship between the two new stereocenters is consistent with the open transition structure arrangement discussed earlier. The E enol ether is presumed to arise from a small amount of S stannane present in the starting material. Addition of (S)-15 to (S)-14 proceeds slowly and produces a mixture of five products of which the E enol ether is the major one. Thus the S aldehyde and the R stannane represent a matched pair whereas the S aldehyde and the S stannane are mismatched.



In contrast to the above example, products with E enol ethers are predominant in reactions between achiral aldehydes and  $\alpha$ -(alkoxy)allylstannanes. Therefore, this example shows that small changes in aldehyde structure can lead to significant changes in product stereostructure. Since all reported cases of electrophilic additions to chiral allylic stannanes proceed by an exclusive anti  $S_{E'}$  pathway, the product configurational change corresponds to variations in the transition structure arrangement. This result is consistent with an earlier conclusion that the various staggered rotamers of the transition structures differ only slightly in energy. (22)

When an aldehyde with both an  $\alpha$ - and a  $\beta$ -chiral center is allowed to react with racemic  $\alpha$ -(alkoxy)allylstannane 15, a mixture of products is isolated (Eq. 39). The addition product is the E enol ether (45%). The configuration of this adduct conforms to the usual pattern of facial selection, i.e., Felkin-Anh control with respect to the aldehyde and syn selectivity with respect to the newly formed two stereocenters. Other products include the recovered aldehyde 16 (40%) and the optically active  $\gamma$ -alkoxy allylic stannane (50%). A kinetic resolution occurs in which only (S)-15 reacts with aldehyde 16. The  $\gamma$ -alkoxy allylic stannane is produced via a stereospecific 1,3-migration of tributyltin, which is discussed in the next section. The  $\alpha$ -S- $\beta$ -R aldehyde 16 reacts with the reagent S stannane but not the R stannane. Since the  $\alpha$ -S aldehyde 14 and the R stannane are a matched pair in asymmetric induction, this result

suggests that the  $\beta$  stereocenter plays a role in determining the outcome of the reaction. However, it is not a deciding role as in those reactions that employ achiral allylstannanes. (17) The E enol ether double bond of the adduct is more in line with additions involving achiral aldehydes.

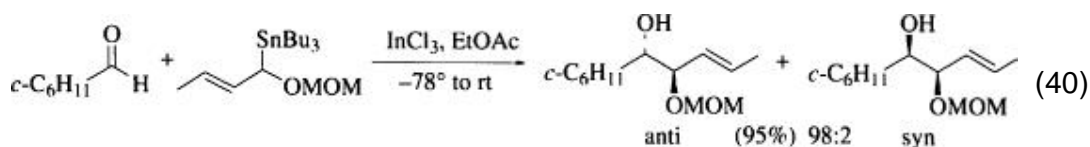


Racemic  $\alpha$ -(alkoxy)allylstannanes are easily prepared by addition of  $\text{Bu}_3\text{SnLi}$  to an  $\alpha, \beta$ -unsaturated aldehyde followed by protection of the resulting hydroxy group. However, the preparation of enantiomerically pure  $\alpha$ -(alkoxy)allylstannanes requires a laborious procedure. The diastereofacial selectivity in a reagent-controlled reaction is moderate. Chiral allylboranes and boronates may be a better choice if a reagent-controlled asymmetric induction is required.

### 3.2.1.5. Transmetalation Followed by Addition

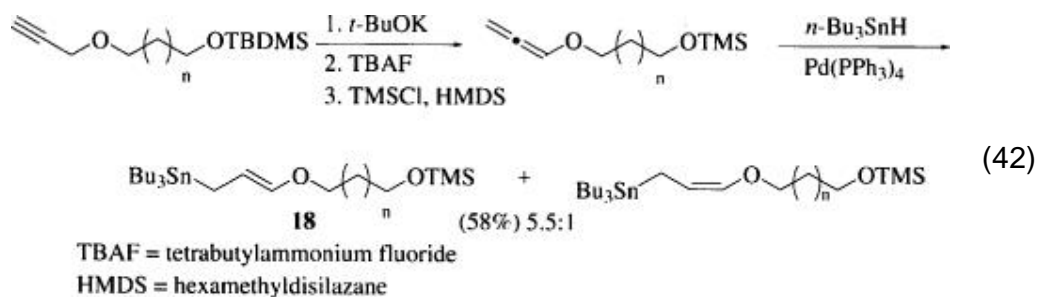
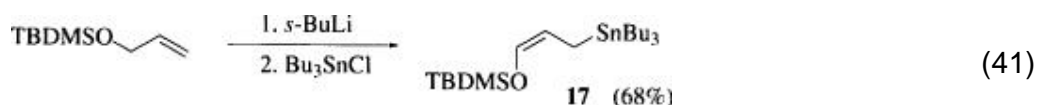
#### 3.2.1.5.1. Reactions Promoted by $\text{InCl}_3$

$\text{InCl}_3$  is found to effect a stereospecific anti  $\text{S}_{\text{E}}2$  transmetalation of alkoxy stannanes to give a transient allylindium reagent, which adds stereoselectively to aldehydes yielding anti adducts. (83) Ethyl acetate is found to be a superior solvent for this reaction. While 2-butenyl(tributyl)stannane (1) reacts with aldehydes under these conditions through a more stable 2-butenylindium species, the  $\alpha$ -alkoxy stannanes react through 3-butenyl-2-yl indium species. Apparently the alkoxy group slows the rate of 1,3-migration of the indium. The chirality of the alkoxy stannanes is effectively transferred to the products. These findings allow direct access to monoprotected 1,2-anti diols (Eq. 40) and expand the scope of the reactions of  $\alpha$ -alkoxy-2-butenyl(tributyl)stannanes. The utility of this reaction is demonstrated in the stereoselective synthesis of four of the eight possible isomers of hexose precursors. (83) In each case, reagent control is a dominant factor in determining product stereochemistry.



### 3.3. Reactions of Achiral $\gamma$ -(Alkoxy)- and $\gamma$ -(Silyloxy)Allylstannane Reagents

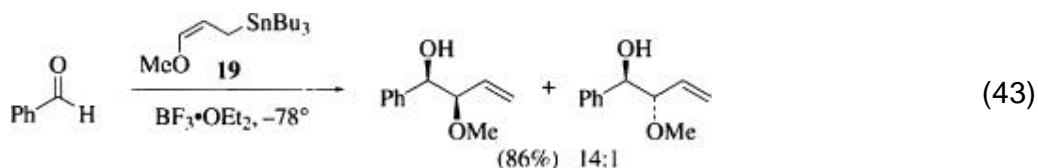
3.3.1.1. Preparation of  $\gamma$ -(Alkoxy)- and  $\gamma$ -(Silyloxy)Allylstannane Reagents  
 Simple Z  $\gamma$ -alkoxy and  $\gamma$ -silyloxyallylstannane reagents **17** are prepared by lithiation of the allylic ether and subsequent addition of  $\text{Bu}_3\text{SnCl}$  (Eq. 41). (84)  
 Preparation of the corresponding E isomers **18** is more difficult, but can be effected through addition of  $\text{Bu}_3\text{SnH}$  to an allenyl ether in the presence of a palladium catalyst (Eq. 42). (85)



#### 3.3.1.2. Lewis Acid Promoted Reactions

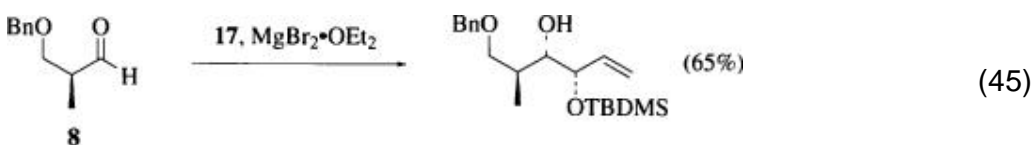
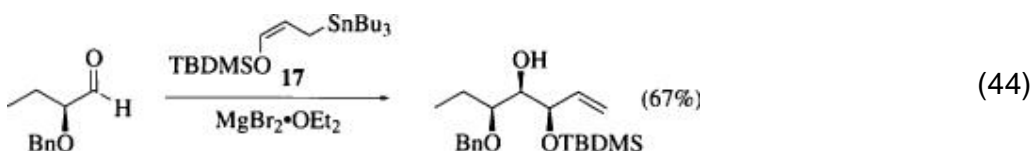
##### 3.3.1.2.1. Reactions with Achiral Aldehydes

While the addition of 2-butenylstannanes to aldehydes produces homoallylic alcohols, which are useful in the preparation of polypropionates (polyketides), the addition of  $\gamma$ -(alkoxy)allylstannanes to aldehydes gives monoprotected 1,2-diols, as illustrated by the addition of  $\gamma$ -(methoxy)allylstannane **19** to benzaldehyde (Eq. 43). (86) The diols are useful intermediates for the preparation of carbohydrates and other polyhydroxy natural products. The reactions of ( $\gamma$ -methoxy)allylstannanes with both aromatic and aliphatic aldehydes have been reported. (86) By analogy to simple 2-butenylstannanes, mainly syn adducts are isolated with all aldehydes in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$  at  $-78^\circ$ .

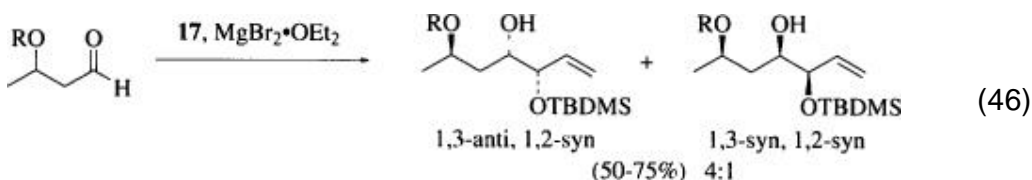


### 3.3.1.2.2. Reactions with Chiral Aldehydes

The reactions of  $\gamma$ -(silyloxy)allylstannane **17** with both  $\alpha$ -alkoxy and  $\alpha$ -methyl aldehydes in the presence of  $\text{MgBr}_2$  have been studied (Eqs. 44 and 45). (84) With  $\alpha$ -substituted aldehydes, the products are the syn, syn adduct for the  $\alpha$ -alkoxy aldehyde and the syn, anti isomer for the  $\alpha$ -methyl aldehyde **8**. In both cases the observed products arise by attack of the allylic stannane on a  $\text{MgBr}_2$ -chelated aldehyde.

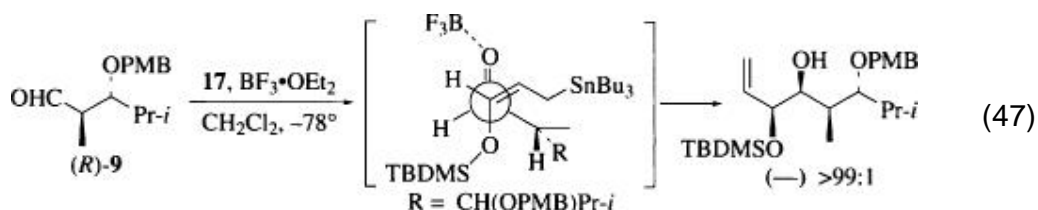


Diminished selectivity is observed for  $\beta$ -alkoxy aldehydes (Eq. 46). The major isomer arises from 1,3-anti asymmetric induction, which is consistent with both a chelation-controlled model and Evans' dipolar model. (17) The 1,2-syn diol relationship in the products is consistent with the acyclic transition structure described earlier.

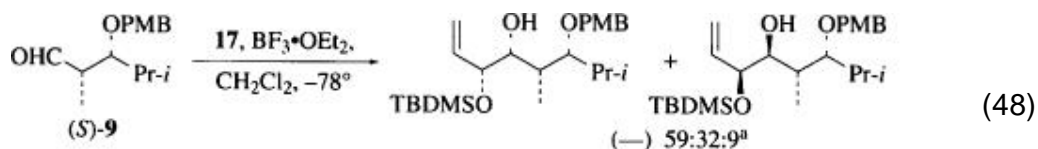


The reactions of  $\gamma$ -(silyloxy)allylstannane **17** with aldehydes possessing both an  $\alpha$  and a  $\beta$  stereocenter with the use of  $\text{BF}_3 \cdot \text{OEt}_2$  as the promoter have been reported. With anti  $\beta$ -branched aldehyde (*R*)-**9**, merged 1,2- and 1,3-asymmetric induction is observed (Eq. 47), similar to the reaction observed for simple allylstannanes (vide infra). (17) Namely, 1,2-asymmetric induction

follows the Felkin-Anh model and 1,3-asymmetric induction follows the dipolar model. The major syn, syn, anti product is favored by >99:1.



With syn  $\beta$ -branched aldehyde (*S*)-**9** under the same conditions, the reaction gives a mixture of three isomers (ratio = 59:32:9) with the major product being the all syn isomer (Eq. 48). In this case the two stereocenters of the aldehyde are biased in opposite directions for attack on the carbonyl group. In contrast to reactions involving simple allylstannanes, the  $\alpha$ -stereo center of aldehyde substrates is more important in determining the outcome of the facial attack (Felkin-Anh control), even with a small Lewis acid for reactions of  $\gamma$ -oxygenated stannanes. This change in  $\pi$ -facial selection from simple allylstannanes to ( $\gamma$ -silyloxy)allylstannanes is attributed to the steric bulk of the TBDMSO group of stannane **17**. Thus, either an increase in the size of the Lewis acid or an increase in the size of the nucleophile can enhance the facial selectivity controlled by the aldehyde  $\alpha$ -stereo center.

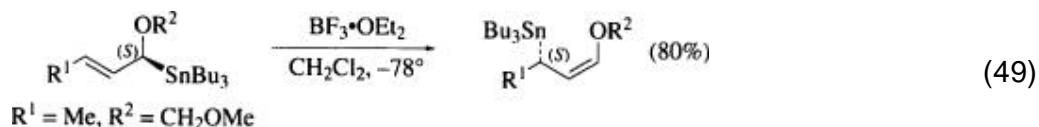


<sup>a</sup> The third unpictured product is the Felkin-Anh 3,4-*anti* diastereomer.

### 3.4. Reactions of Chiral $\gamma$ -(Alkoxy) and $\gamma$ -(Silyloxy)Allylstannane Reagents

#### 3.4.1.1. Preparation of Enantioenriched $\gamma$ -(Alkoxy) and $\gamma$ -(Silyloxy)Allylstannane Reagents

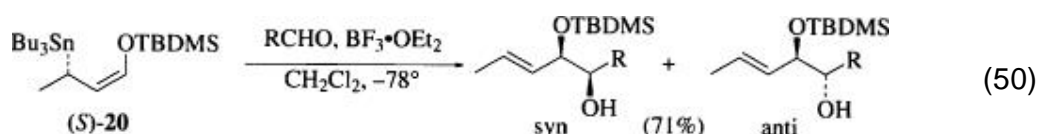
In the absence of a reactive aldehyde,  $\alpha$ -(alkoxy)allylstannanes are isomerized by  $\text{BF}_3 \cdot \text{OEt}_2$  to *Z*  $\gamma$ -(alkoxy)allylic stannanes (Eq. 49). (87) This isomerization proceeds by an intermolecular pathway with allylic and configurational inversion. (72) This discovery opened an efficient entry to enantiomerically enriched  $\gamma$ -(alkoxy)- and  $\gamma$ -(silyloxy)allylstannane reagents.



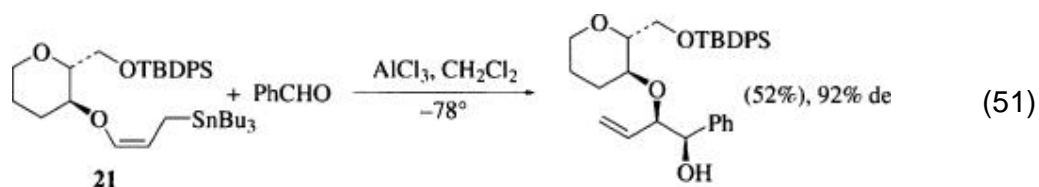
### 3.4.1.2. Lewis Acid Promoted Reactions

#### 3.4.1.2.1. Reactions with Achiral Aldehydes

When the  $\gamma$ -(alkoxy)allylstannane **20** is reacted with aldehydes in the presence of a Lewis acid, mainly syn monoprotected 1,2-diols are isolated (Eq. 50). (6) These reactions proceed stereospecifically by an anti  $\text{S}_{\text{E}}2$  pathway, similar to the pathway described for simple allylstannanes. The enantiomeric purity of the product is equal to that of the starting stannane. This method has been applied in natural product total synthesis as discussed in the section entitled Applications in Synthesis.



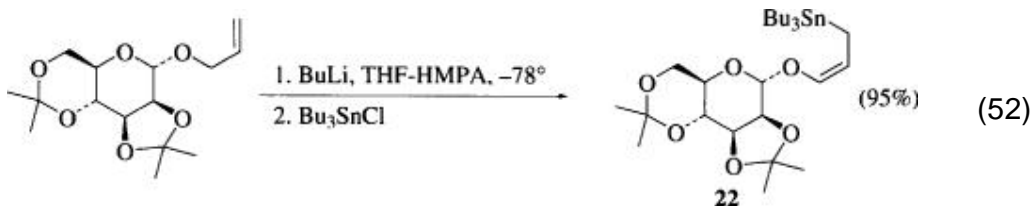
The reaction of the chiral  $\gamma$ -(alkoxy)allylstannane **21** with aldehydes in the presence of a Lewis acid entails a synthesis of syn 1,2-diol derivatives (Eq. 51). (88) Both aromatic and aliphatic aldehydes afford syn adducts with diastereoselectivities greater than 97:3 in reactions promoted by  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{AlCl}_3$ , or  $\text{AlCl}_3 \cdot \text{OEt}_2$ . The use of  $\text{TiCl}_4$  and  $\text{SnCl}_4$  gives unsatisfactory results. The diastereoselectivity is highest when  $\text{AlCl}_3$  or  $\text{AlCl}_3 \cdot \text{OEt}_2$  is used, whereas  $\text{BF}_3 \cdot \text{OEt}_2$  leads to slightly decreased selectivity.



The mannose-derived  $\gamma$ -(alkoxy)allylstannane **22** is prepared from allyl 2,3:5,6-di-O-isopropylidene- $\alpha$ -D-mannopyranoside by metalation with *n*-BuLi in THF-HMPA at  $-78^\circ$  followed by treatment of the allyl anion with  $\text{Bu}_3\text{SnCl}$  (Eq. 52). (89) This  $\gamma$ -(alkoxy)allylstannane is reported to give modest

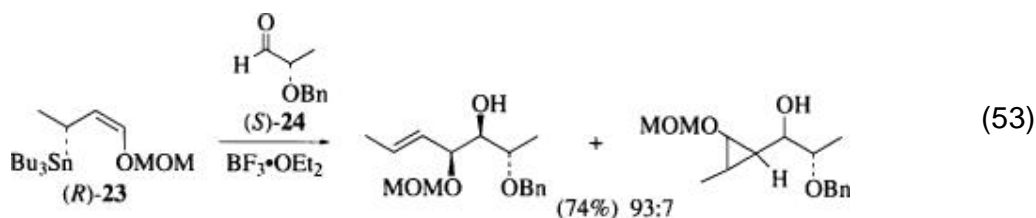


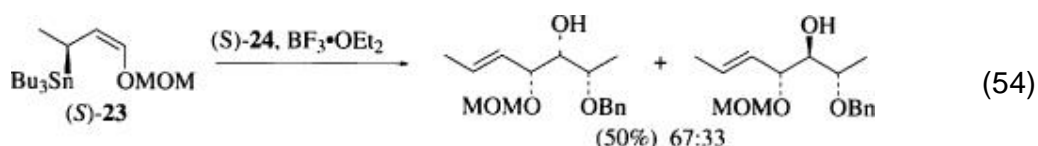
diastereoselectivity (ratio = 7:1) when reacted with  $\alpha$ -(benzyloxy)acetaldehyde in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$ , and high selectivity with chiral aldehydes. (89) The configuration of the major product deriving from the  $\text{BF}_3 \cdot \text{OEt}_2$  catalyzed reaction is suggested to result from an acyclic transition structure pathway.



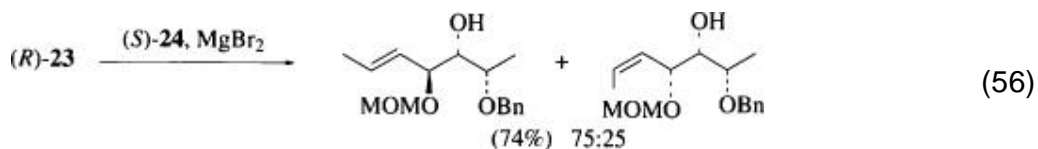
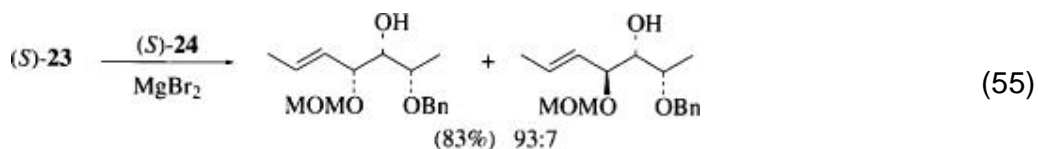
#### 3.4.1.2.2. Reactions with Chiral Aldehydes

Reactions of  $\gamma$ -(alkoxy)- and  $\gamma$ -(silyloxy)allylstannane reagents and (*S*)-2-(benzyloxy)propanal (**24**) with Lewis acids  $\text{BF}_3 \cdot \text{OEt}_2$  and  $\text{MgBr}_2$  as the promoters have been studied (Eqs. 53–56). (90, 91) In the  $\text{BF}_3 \cdot \text{OEt}_2$  promoted reaction, the *R* stannane and the *S* aldehyde exhibit matching pair characteristics (Eq. 53). Addition of the (MOM)oxystannane (*R*)-**23** to propanal **24** in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$  gives a 93:7 mixture of *E* syn, anti alcohol and cyclopropyl adduct in 74% yield. On the other hand, the stannane (*S*)-**23** affords a 67:33 mixture of *E* syn, syn and *E* anti, anti diastereomers upon addition of the *S* aldehyde (Eq. 54). The matched pair reaction is proposed to be consistent with an anti  $\text{S}_{\text{E}}'$  pathway. The *E* geometry of the product indicates a preferred *E* arrangement of the incipient double bond in the transition state. With these two constraints, the transition structure is suggested to have the  $\text{C}=\text{O}$  and the  $\text{C}=\text{C}$  assume an antiperiplanar relationship. The diastereofacial selection with respect to (*S*)-2-(benzyloxy)-propanal (**24**) is consistent with the Felkin-Anh model. The  $\text{BF}_3 \cdot \text{OEt}_2$  promoted addition of  $\gamma$ -(silyloxy) and  $\gamma$ -(alkoxy)allylstannanes (e.g. **23**) to aldehyde **24** is proposed to be under reagent control.

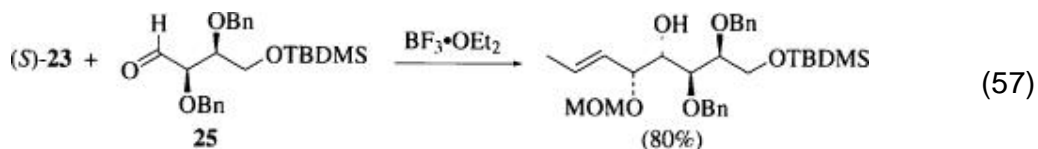




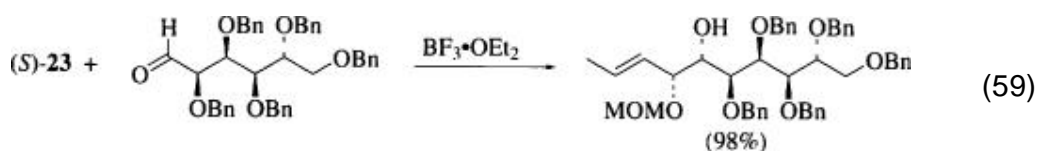
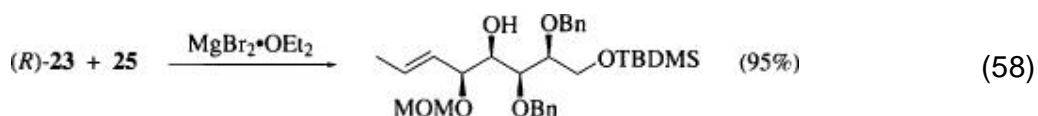
Addition of the  $\gamma$ -(alkoxy)allylstannanes **23** to aldehyde **24** in the presence of  $\text{MgBr}_2$  proceeds slowly to give a reversed matched/mismatched pair (Eqs. **55** and **56**). A 93:7 mixture of E syn, syn and E anti, syn alcohols is obtained in the reaction of the S stannane and (S)-**24**. The corresponding R stannane gives a 75:25 mixture of E anti, syn and Z syn, syn alcohols. The major product of Eq. **55** arises from chelation control while the major isomer of Eq. **56** is consistent with Felkin-Anh selection.



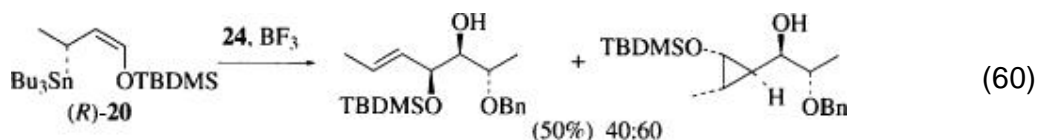
When the S stannane **23** reacts with the tartrate-derived aldehyde **25** in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$ , the only detectable product is the syn, anti, syn alcohol (Eq. **57**). The aldehyde **25** has an  $\alpha$ -R chiral center. All three stereogenic centers in the starting materials favor the same stereochemical path in this reaction. However, examination of a model transition structure indicates a mutual exclusion of Felkin-Anh and Evans' dipolar models for this reaction. A combination of Cornforth model for 1,2-asymmetric induction and Evans' model for 1,3-asymmetric induction appears to be more reasonable. (**92**) Further studies are needed to clarify the true transition structure.



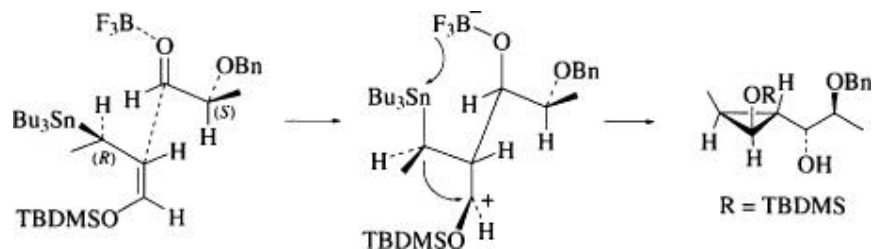
Several other matched pairings were also examined. The tartrate-derived aldehyde **25** affords the syn, syn, syn alcohol as the only detectable product upon  $\text{MgBr}_2$  promoted reaction with the stannane (*R*)-**23** (Eq. 58). This reaction proceeds by chelation control and matched pairing of stannane and aldehyde. Addition of stannane (*S*)-**23** to pentabenzylglucose yields a single alcohol in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$  (Eq. 59). This reaction follows Felkin-Anh selection with regard to aldehyde facial differentiation. The *S* stannane reagent greatly enhances the stereoselectivity by matched double asymmetric induction.



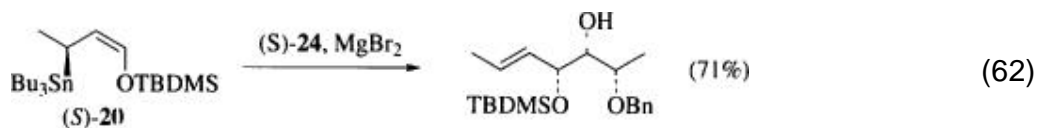
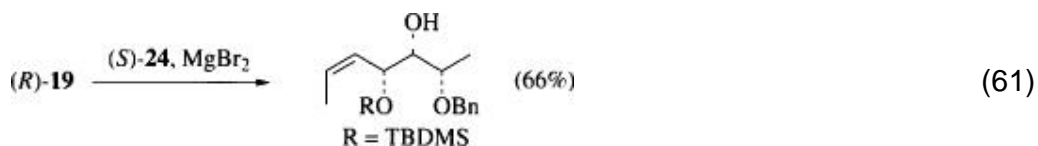
Protecting groups appear to play a significant role in the outcome of these reactions. Up to 60% of the total adduct is the cyclopropylcarbinol when the  $\gamma$  oxygen of the stannane reagent is protected as a TBDMS ether (Eq. 60). (91) A 40:60 mixture of the *E* syn, anti adduct and the cyclopropylcarbinol is isolated when the protected stannane (*R*)-**20** is reacted with (*S*)-2-(benzyloxy)propanal (**24**) in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$ . The cyclopropylcarbinol is suggested to arise by the initial attack of the enol ether double bond on the aldehyde- $\text{BF}_3 \cdot \text{OEt}_2$  complex followed by 1,3-nucleophilic ring closure of the intermediate carbocation (Figure 2).



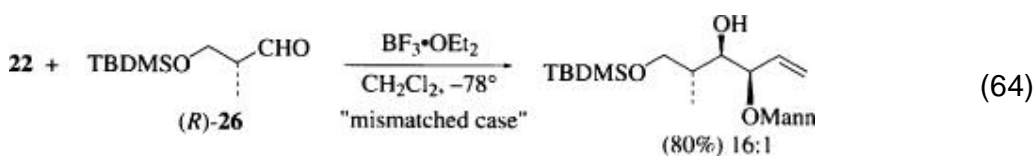
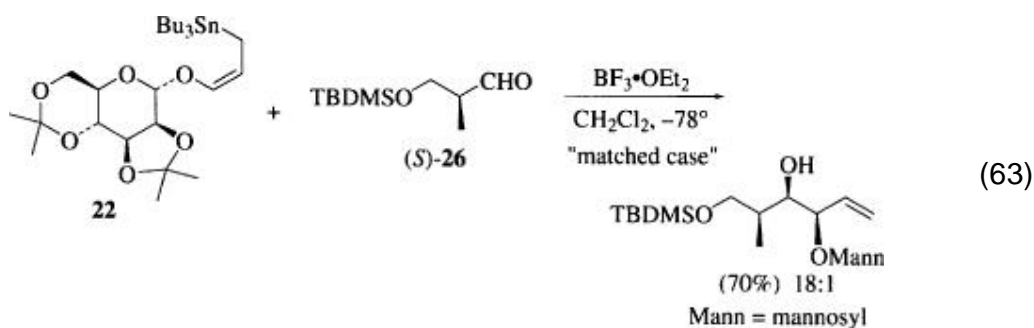
**Figure 2.** Reaction pathways leading to cyclopropane from stannane (*R*)-**20**.



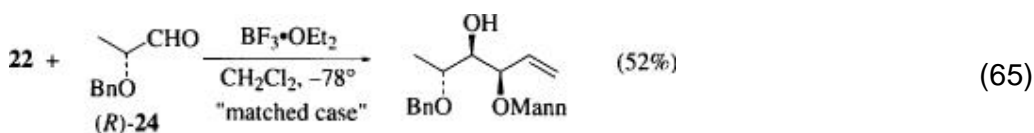
When stannanes **20** react with aldehyde (*S*)-**24** in the presence of  $\text{MgBr}_2$ , only one product is isolated for each reaction. Stannane (*R*)-**20** gives the *Z* syn, syn adduct (Eq. 61) while stannane (*S*)-**20** produces the *E* syn, syn adduct (Eq. 62). The  $\text{MgBr}_2$  promoted addition of  $\gamma$ -(silyloxy)allylstannanes **20** to (*S*)-**24** is proposed to proceed under substrate control. The Cram chelation control products are produced regardless of the stannane configuration. The *S* stannane is matched to the *S* aldehyde.



High diastereoselectivity is observed when the carbohydrate-derived  $\gamma$ -(alkoxy)allylstannane **22** is reacted with the  $\beta$ -alkoxy- $\alpha$ -methylpropionaldehyde **26**. (89) Double asymmetric reactions of **22** with both enantiomers of chiral aldehyde **26** were examined (Eqs. 63 and 64). In the presence of  $\text{BF}_3 \cdot \text{OEt}_2$ , the facial selectivity of stannane **22** is sufficient to completely overcome the intrinsic diastereofacial bias of (*R*)-**26** in the mismatched pair giving a 16:1 mixture in favor of the anti, syn isomer (Eq. 64). (89) The matched pair gives an 18:1 mixture in favor of the syn, syn isomer (Eq. 63). The chiral stannane is able to dominate the outcome of the reaction since the intrinsic diastereofacial selectivity of the aldehyde is not overwhelmingly high.

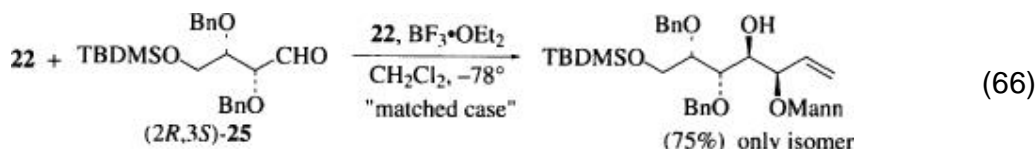


Double asymmetric reactions of stannane **22** with aldehydes (*R*)- and (*S*)-**24** were also examined. The  $\text{BF}_3 \cdot \text{OEt}_2$  promoted matched reaction of stannane **22** with aldehyde (*R*)-**24** gives the anti, syn product as the only diastereomer (Eq. **65**). (89) The mismatched pair involving stannane **22** and aldehyde (*S*)-**24** gives the all syn diastereomer as the major component of a 5:1 mixture. Selectivity in the mismatched pair is increased to 7:1 by using a TBDMS-protected lactaldehyde analog of (*S*)-**24** as the substrate. The major product of the mismatched pair is assumed to arise via a synclinal transition structure, in which aldehyde **24** adopts an anti-Felkin-Anh conformation. This example shows the high enantioselectivity of the chiral stannane reagent **22**, which overcomes the usual  $\pi$  facial preference of the  $\alpha$ -alkoxy aldehyde to react by way of the Felkin-Anh transition structure.

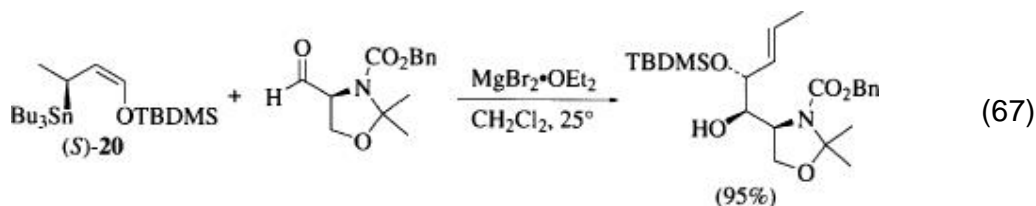


Double asymmetric reactions of stannane **22** were further examined with the tartrate-derived aldehydes (*2R,3S*)- and (*2S,3R*)-**25** (Eq. **66**). (89) The  $\text{BF}_3 \cdot \text{OEt}_2$ -promoted matched reaction of stannane **22** with aldehyde (*2R,3R*)-**25** gives the syn, anti, syn product as the only diastereomer. This result is similar to the reaction with stannane **23** in that no other isomer is identified in this asymmetric reaction. The mismatched pair involving stannane

**22** and aldehyde (2*S*,3*R*)-**25** gives the all syn diastereomer as the major component of a 2:1 mixture. The diminished selectivity with aldehyde (2*S*,3*R*)-**25** is attributed to its increased intrinsic diastereofacial preference. This increased preference may arise from a combination of a merged 1,2- and 1,3-  $\pi$  facial bias. (17) The stannane reagent is required to overcome both of these preferences in order to produce the all syn isomer.



The reaction between  $\gamma$ -silyoxy- $\alpha$ -methylallylstannane (*S*)-**20** and a serine-derived aldehyde in the presence of  $\text{MgBr}_2$  has been studied (Eq. 67). (93) The aldehyde was mixed with  $\text{MgBr}_2$  at  $-20^\circ$  followed by slow addition of stannane **20**. Upon warming to  $25^\circ$ , stannane addition to the aldehyde occurs to afford the monoprotected diol in near quantitative yield with  $>10:1$  selectivity for the syn diastereomer. Adding 2.3 equivalents of the racemic stannane to the aldehyde effects a useful level of kinetic resolution ( $>10:1$  S/R), thus avoiding the need to prepare the enantiomerically pure  $\gamma$ -(alkoxy)stannane. Both reagents **20** and **22** are useful in the preparation of enantiomerically enriched monoprotected 1,2-diols. However the relatively lengthy preparation of these reagents may hinder widespread applications.



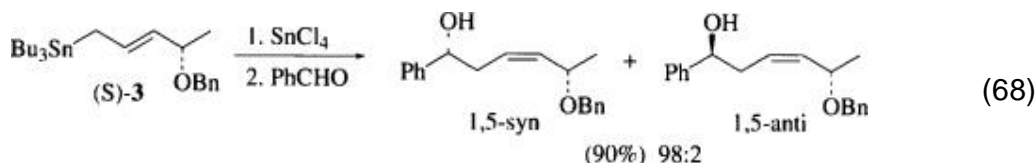
### 3.5. Reactions of 4-Alkoxy-2-pentenylstannane Reagents

#### 3.5.1.1. Transmetalation Followed by Addition

##### 3.5.1.1.1. Reactions with Achiral Aldehydes

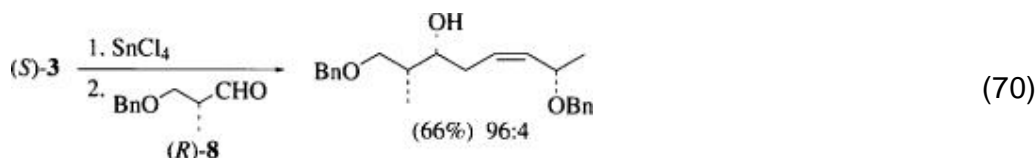
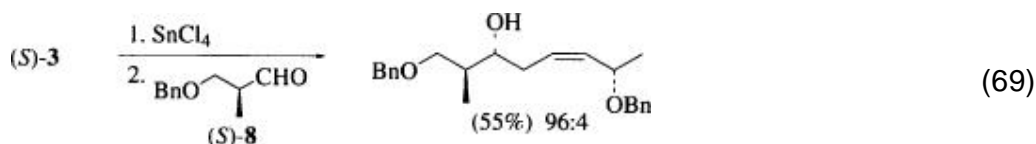
The reactions of 4-(alkoxy)pentenylstannanes, such as (*S*)-**3**, with various aldehydes to introduce a new stereocenter at a remote position have been extensively studied. (21) The stannane reagents undergo transmetalation with  $\text{SnCl}_4$  prior to addition to aldehydes. (12) With both aromatic and aliphatic achiral aldehydes, the major product is the *Z* alkene with a 1,5-syn relationship

for the two stereocenters. The diastereoselectivity for the reactions with achiral aldehydes is in the range 92:8 to 98:2 (Eq. 68).



### 3.5.1.1.2. Reactions with Chiral Aldehydes

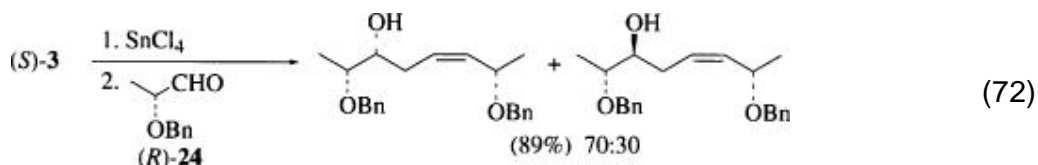
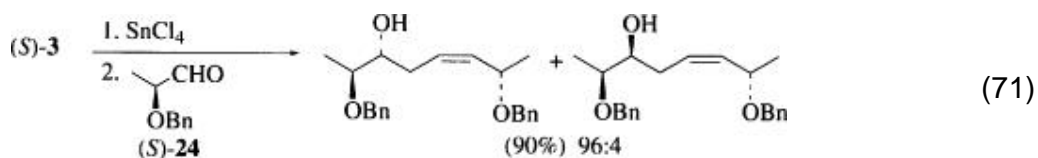
Double asymmetric synthesis using stannane **3** with chiral aldehydes has been studied to evaluate the synthetic utility of the reagent. Under standard conditions, stannane (*S*)-**3** completely overcomes the  $\pi$ -facial bias of aldehyde **8** (Eq. 69). The reaction of stannane (*S*)-**3** with aldehyde (*S*)-**8** gives the anti product as the major component while the same reaction with (*R*)-**8** gives the syn product as the major component of a 96:4 mixture (Eq. 70).



Chelation control does not seem to be in effect in these reactions. The results support the intermediacy of an internally coordinated trichlorostannane (see Eq. 11). Coordination of the aldehyde oxygen to the internally coordinated tin atom saturates the six coordination sites of the tin atom.

Matching and mismatching characteristics are observed for the reactions of stannane (*S*)-**3** and chiral aldehyde **24**. (12) The matched pair appears to be (*S*)-**3** and (*S*)-**24**, which react to produce the anti product as the major component of a 96:4 mixture (Eq. 71). The reaction between stannane (*S*)-**3** and aldehyde (*R*)-**24** gives the syn product as the major component of a 70:30 mixture (Eq. 72). In both reactions, the minor diastereomer has the 1,5-anti relationship, which is suggested to arise from equilibration of the trichlorostannane intermediate. The formation of the 1,5-syn product in these

reactions implies initial transmetalation of the stannane to the allylic tin trichloride, which is stabilized by coordination of the benzyloxy group to the electron-deficient tin atom (Eq. 11). The coordination complex is formed stereoselectively so that the methyl and vinyl groups are trans-disposed about the four-membered ring. The allylic tin trichloride then reacts with the aldehyde, which is added 5 minutes after the allylstannane and SnCl<sub>4</sub> are mixed. A six-membered, chair-like, cyclic transition structure controls the facial selectivity of the reaction. However the intermediate allylic tin trichloride may racemize through 1,3-tin migration when its addition to the aldehyde is relatively slow. This is suggested to account for the formation of the minor diastereomer.



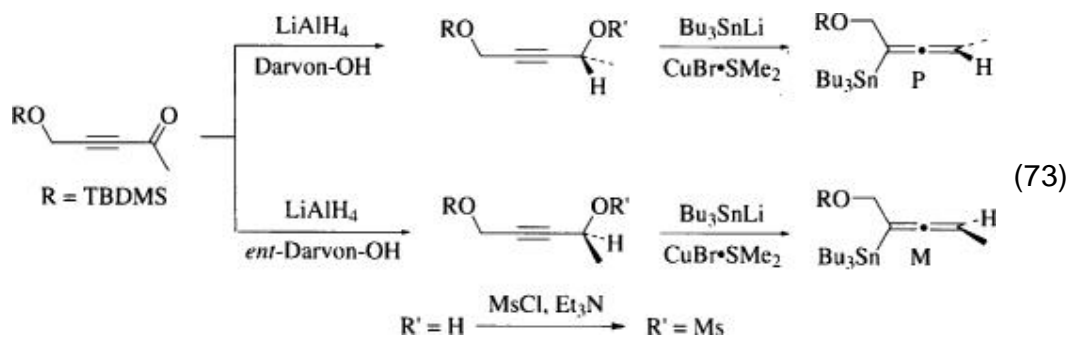
Application of a  $\delta$ -(alkoxy)allylstannane has been found in the total synthesis of ( $\pm$ )-patulolide C. If a 1,5-syn diol structure unit is the desired target one should consider using this reagent.

### 3.6. Reactions of Allenylstannane Reagents

#### 3.6.1.1. Preparation of Allenylstannane Reagents

When propargylic mesylates are treated with Bu<sub>3</sub>SnLi in the presence of an equimolar amount of CuBr<sub>2</sub>·SMe<sub>2</sub>, an S<sub>N</sub>2' reaction occurs to afford allenylstannanes. (94, 95) Enantioenriched mesylates are obtained by asymmetric reduction of propargylic ketones with ChiralD reagent. The stereochemical nomenclature of chiral allenes cited in this review follows the recommendations of Prelog and Helmchen (Eq. 73). (96)

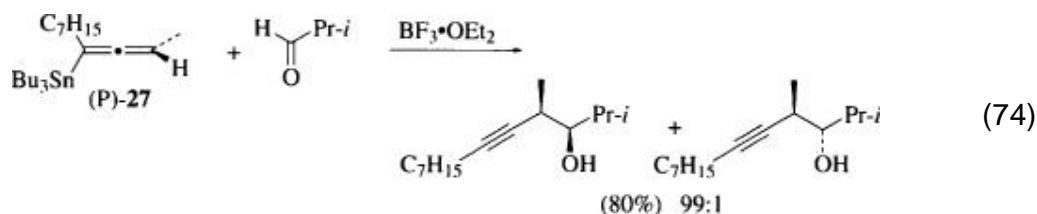




### 3.6.2.1. Lewis Acid Promoted Reactions

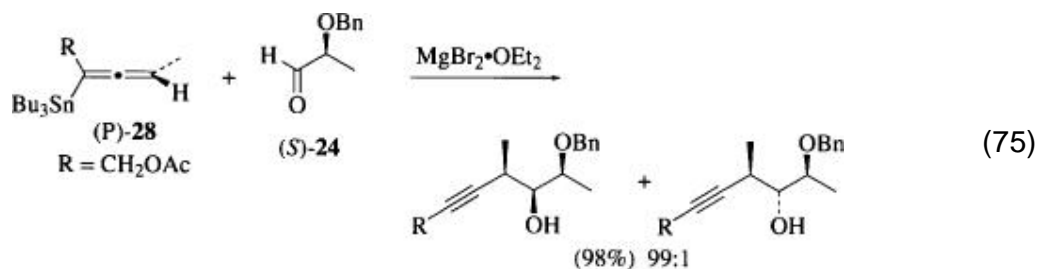
#### 3.6.2.1.1. Reactions with Achiral Aldehydes

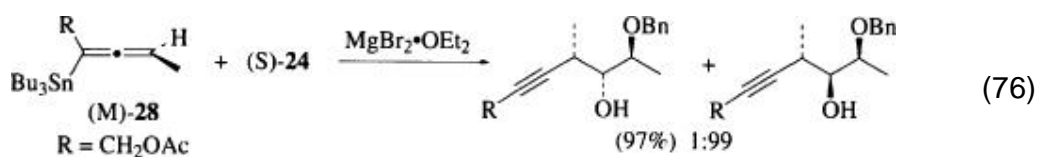
The reactions of allenylstannanes, e.g., **27**, with  $\alpha$ -branched aldehydes in the presence of equimolar  $\text{BF}_3 \cdot \text{OEt}_2$  afford mainly syn adducts (Eq. **74**). With straight-chain aldehydes a mixture of both anti and syn isomers is produced with the anti isomer slightly in excess. (**94**, **97**)



#### 3.6.2.1.2. Reactions with Chiral Aldehydes

Chiral allenylstannane (P)-**28** adds to (S)- $\alpha$ -benzyloxy propanal (**24**) to afford the syn, syn adduct exclusively in the presence of  $\text{MgBr}_2 \cdot \text{OEt}_2$  (Eq. **75**). The same reaction pair is less selective when  $\text{BF}_3 \cdot \text{OEt}_2$  is used as the promoter. However, the enantiomeric allenylstannane (M)-**28** adds to (S)-**24** to afford predominantly the anti, syn adduct in the presence of  $\text{MgBr}_2 \cdot \text{OEt}_2$  (Eq. **76**) and the syn, syn adduct in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$ . (**94**)

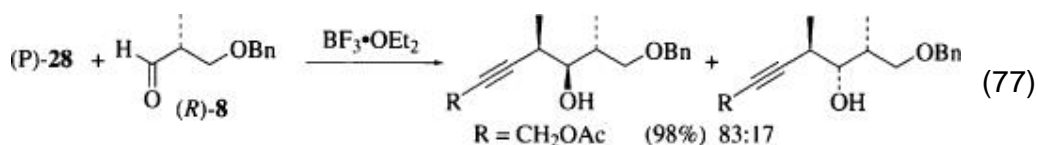


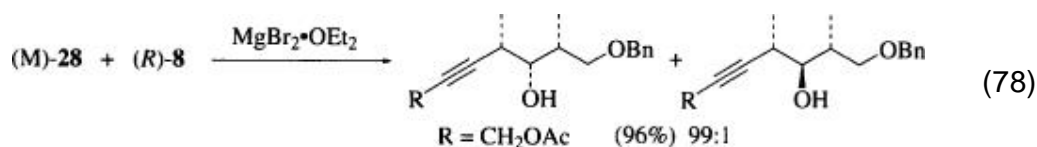


In  $\text{BF}_3 \cdot \text{OEt}_2$  promoted additions, the major product comes from attack by the allenylstannane on the *si*-face of the S aldehyde (anti-Felkin-Anh approach), a mismatched pairing. The favored reaction pairing is accounted for by a transition structure in which the S aldehyde is juxtaposed to follow either the Cornforth dipolar model or the Felkin-Anh model.

The  $\text{MgBr}_2 \cdot \text{OEt}_2$  promoted reactions are proposed to proceed through chelated transition structures. The intrinsic bias of the chiral aldehyde is enhanced by this chelation. The vinyl hydrogen of the stannane preferentially assumes a position over the most congested region of the chelate to minimize steric repulsion. As in allylstannane additions, the  $\text{Bu}_3\text{Sn}$  grouping is oriented anti to the forming C - C bond. In order to satisfy these stereoelectronic constraints, the M stannane reagents must assume orientations that lead to anti adducts. Anti adducts are rarely formed in Lewis acid promoted additions of related allylstannanes to aldehydes.

The reactions of P and M allenylstannanes with chiral aldehyde (*R*)-**8** were studied using either  $\text{BF}_3 \cdot \text{OEt}_2$  or  $\text{MgBr}_2 \cdot \text{OEt}_2$  (Eqs. 77 and 78). (94) In the  $\text{BF}_3 \cdot \text{OEt}_2$  promoted additions, stannane (P)-**28** and aldehyde (*R*)-**8** are a mismatched pair, whereas stannane (M)-**28** and aldehyde (*R*)-**8** are stereochemically matched. In the mismatched case, the syn, anti product is favored in the ratio of 84:16 while in the matched case the ratio is >99:1 in favor of the syn, syn isomer. In the  $\text{MgBr}_2 \cdot \text{OEt}_2$  promoted reactions, stannane (P)-**28** adds to aldehyde (*R*)-**8** favoring the syn, anti isomer by >99:1 whereas stannane (M)-**28** affords the syn, syn diastereomer. The absence of the anti, syn-isomer in the addition products suggests the absence of chelation control in contrast to the reactions of  $\alpha$ -(benzyloxy)propanal. Comparison of the results in Eqs. 75 and 76 vs. Eqs. 77 and 78 implies that a five-membered chelate is more stable than a six-membered chelate when  $\text{MgBr}_2$  is used as the Lewis acid.



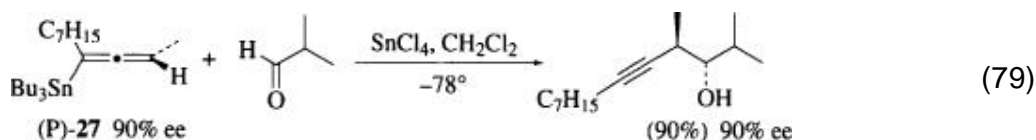


Most allenylmetal reagents are known to be in equilibrium with their propargylic isomers. These chiral allenylstannane reagents represent the first examples of practical applications of allenylmetals in diastereoselective reactions.

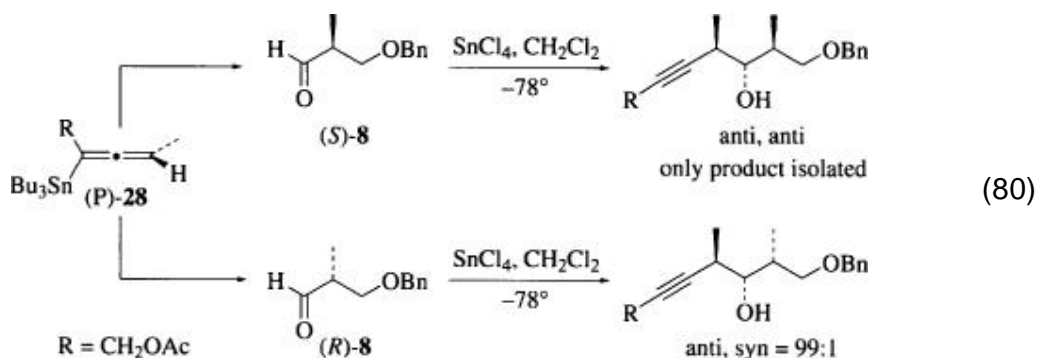
### 3.6.2.2. Transmetalation Followed by Addition

#### 3.6.2.2.1. Reactions Promoted by SnCl<sub>4</sub>

To obtain the anti, syn- and the anti, anti-stereotriads commonly found in natural products, the reactions of allenylstannanes and aldehydes with SnCl<sub>4</sub> as the Lewis acid were examined. (98-100) The anti isomer is obtained when the allenylstannane (P)-27 is mixed with SnCl<sub>4</sub> at -78° in CH<sub>2</sub>Cl<sub>2</sub> prior to addition of the aldehyde (Eq. 79). The reaction proceeds in 90% yield with perfect enantioselectivity.



All four triads are synthesized from allenylstannane (P)-28 and (S)- and (R)-2-methyl-3-(benzyloxy)propanal (8). (100) The syn, syn and syn, anti diastereomers are obtained through the use of BF<sub>3</sub>·OEt<sub>2</sub> and MgBr<sub>2</sub>·OEt<sub>2</sub>. As described earlier, these two isomers arise through acyclic transition structures in which the aldehyde orientation follows the Felkin-Anh and chelation models, respectively. The anti, anti and anti, syn diastereomers are obtained through the use of SnCl<sub>4</sub> with (P)-28 and (S)-8 (Eq. 80).

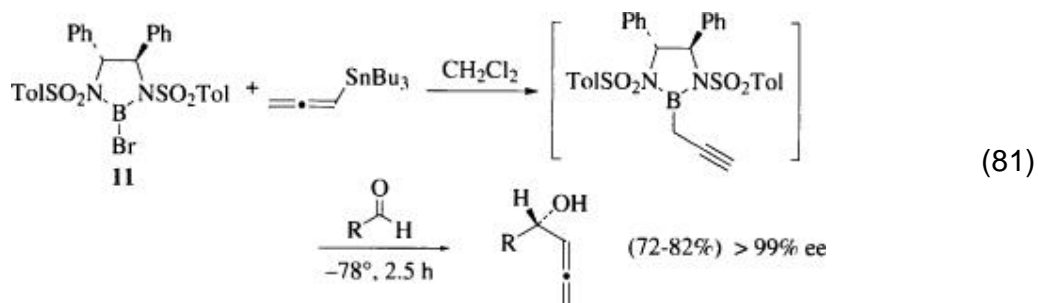


Transmetalation occurs before the addition to aldehydes when  $\text{SnCl}_4$  is used as the promoter. A six-membered, cyclic transition structure is proposed, in which the aldehyde is chelated by  $\text{SnCl}_4$ . The anti, syn diastereomer is also obtained through a six-membered, cyclic transition state in which the aldehyde is not chelated, i.e., attack under Felkin-Anh control. Apparently the interplay between the chiral aldehyde and the allenylstannane is important. Steric effects in the transition states determine whether the aldehyde is chelated. Thus all four triads can be obtained with high diastereofacial selectivity from allenylstannane **28**.

There are other allylmetal reagents such as allylboranes and allylboronates that have proven to be valuable synthetic tools for the preparation of the four stereotriads commonly found in natural products. These newly developed allenylstannane reagents should find their use in total synthesis and should be complementary to existing reagents.

#### 3.6.2.2.2. Reactions Promoted by a Chiral Borane

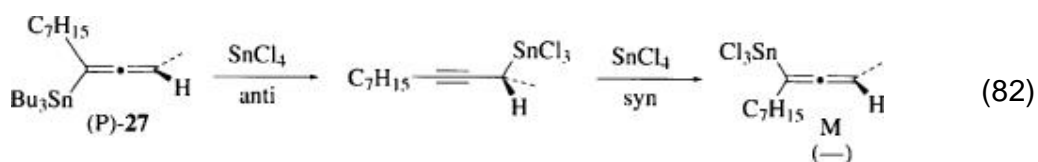
The R,R and S,S isomers of the 1,2-diamino-1,2-diphenylethane derived bromoborane **11** also promote enantioselective reactions of allenylstannanes with aldehydes (Eq. **81**). (**101**) Both aliphatic and aromatic aldehydes can be employed with the allenylstannane to produce allenyl alcohols in good yield and excellent enantioselectivity. A propargylborane intermediate is involved in this reaction. The extraordinary enantioselectivity is rationalized with a cyclic transition state, in which the aldehyde oxygen is associated with the electrophilic boron atom and the chiral controller effectively blocks one  $\pi$ -face of the aldehyde. Under these conditions, the allenylstannane is effectively transmetalated into the propargylic borane intermediate, and the product is the allenyl alcohol.



### 3.7. Reactions of Propargylstannane Reagents

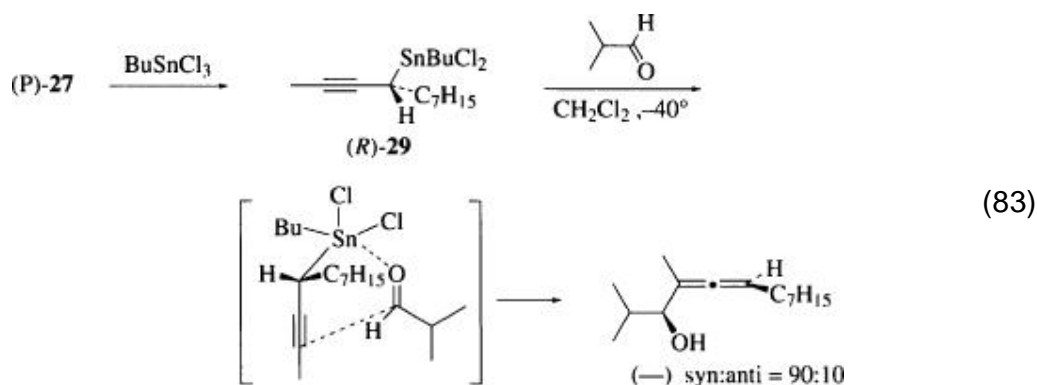
#### 3.7.1.1. Preparation of Propargylstannane Reagents

The addition of  $\text{SnCl}_4$  to allenylstannanes leads to the transient formation of a propargylic chlorostannane by a presumed anti  $\text{S}_{\text{E}}$  transmetalation (Eq. 82). (98) The resulting propargylstannanes isomerize to the more stable allenylstannanes. The overall process proceeds with inversion of allene configuration.



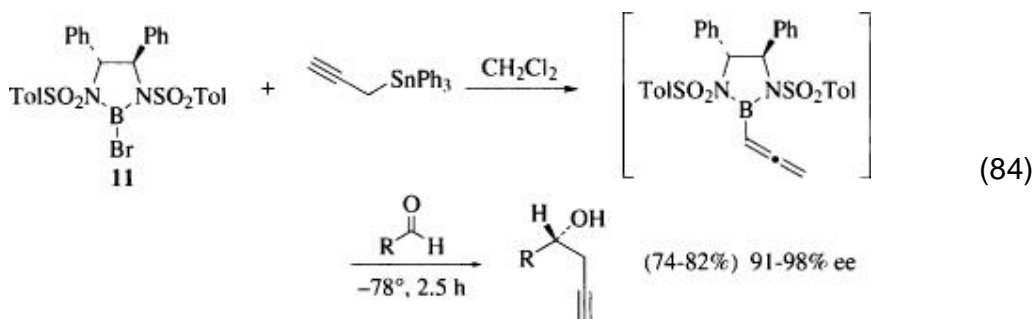
##### 3.7.1.1.1. Reactions Promoted by $\text{BuSnCl}_3$

Replacing  $\text{SnCl}_4$  with  $\text{BuSnCl}_3$  decreases the rate of both transmetalation and isomerization (Eq. 83). (99) With allenylstannane (P)-27, the transformation to propargylic chlorostannane can be monitored by  $^1\text{H}$  NMR spectroscopy. Conversion into propargylic chlorostannane (R)-29 at  $-40^\circ$  is instantaneous, but subsequent isomerization to the allenylstannane requires several hours at room temperature. Thus the product is the allenyl alcohol if an aldehyde is added before the isomerization occurs. The reactions of propargylstannane 29 with  $\alpha$ -branched aldehydes yield allenylcarbinols in a ratio of 90:10 in favor of the syn isomer (Eq. 83). The terms “syn” and “anti” refer to the relationship between the  $\delta$  allenic and the  $\alpha$ -carbinyl hydrogens of the allenylcarbinols. (99) The preferential formation of the syn adduct is explained by a cyclic transition structure as shown in Eq. 83.



### 3.7.1.1.2. Reactions Promoted by a Chiral Borane

Bromoborane **11** also promotes enantioselective reactions of propargylic stannanes with aldehydes (Eq. 84). (101) Both aliphatic and aromatic aldehydes can be employed to produce homopropargylic alcohols in good yield and high enantioselectivity. The reaction is arranged under the heading of propargylic stannanes because propargylic triphenylstannane is used as the reagent. The actual reactive intermediate is an allenylborane species. This procedure produces homopropargyl alcohols in 74–82% yield and 91–98% ee using the chiral controller **11**. Chiral Lewis acid **11** is complementary to chiral allenylstannane reagents **27** in that the products are homopropargyl alcohols without methyl substitution at the propargylic carbon. Therefore each reagent is rather specific for the preparation of a unique type of homopropargylic alcohol.



### 3.8. Intramolecular Reactions of Allyl- and Allenylstannanes

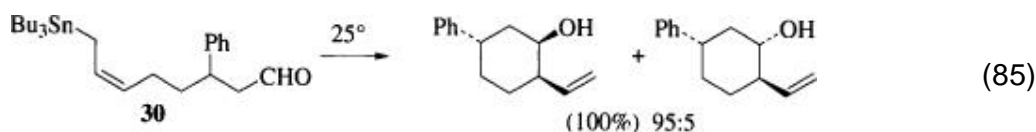
One of the advantages of the stannane reagents is their relative stability toward mild electrophiles such as aldehydes. (22, 25)  $\alpha$ -(Alkoxy)allylstannanes are stable to normal workup procedures and to chromatographic separation. They are not reactive toward the aldehyde function until a Lewis acid is added or the mixture is heated to about 130°.

Because of this stability, it is possible to prepare compounds containing both the allylstannane moiety and the aldehyde function. Intramolecular additions usually are carried out in dilute solutions to avoid intermolecular reactions.

### 3.8.1.1. Reactions Forming Carbocycles

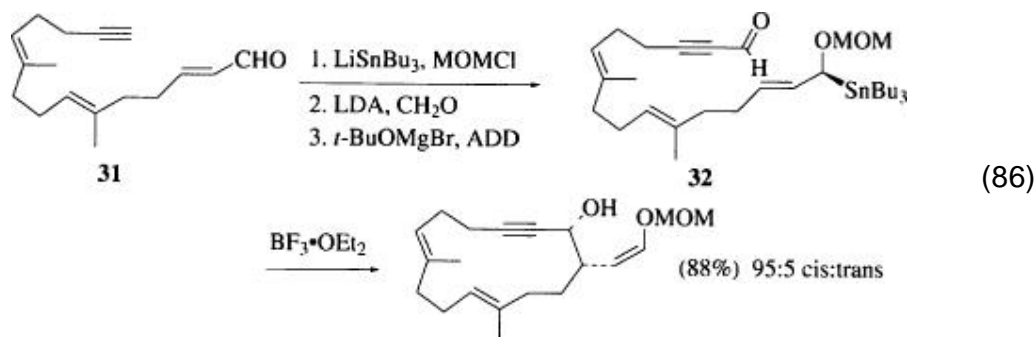
#### 3.8.1.1.1. Thermal Reactions

The cyclization of allylstannanes (*Z*)- and (*E*)-**30** to produce six-membered rings has been examined (Eq. 85). (27) Formation of these rings can be achieved under either thermal or Lewis acidic conditions. As illustrated below, the *Z* stannane preferentially forms the 1,2-*syn* adduct under both thermal and  $\text{BF}_3 \cdot \text{OEt}_2$  conditions. However the *E* stannane affords the 1,2-*anti* adduct as the major isomer when treated with  $\text{BF}_3 \cdot \text{OEt}_2$ . Under thermal conditions the 1,2-*syn* adduct is still the major product. Thermal reactions of allylstannyl aldehydes appear to afford only six-membered rings.

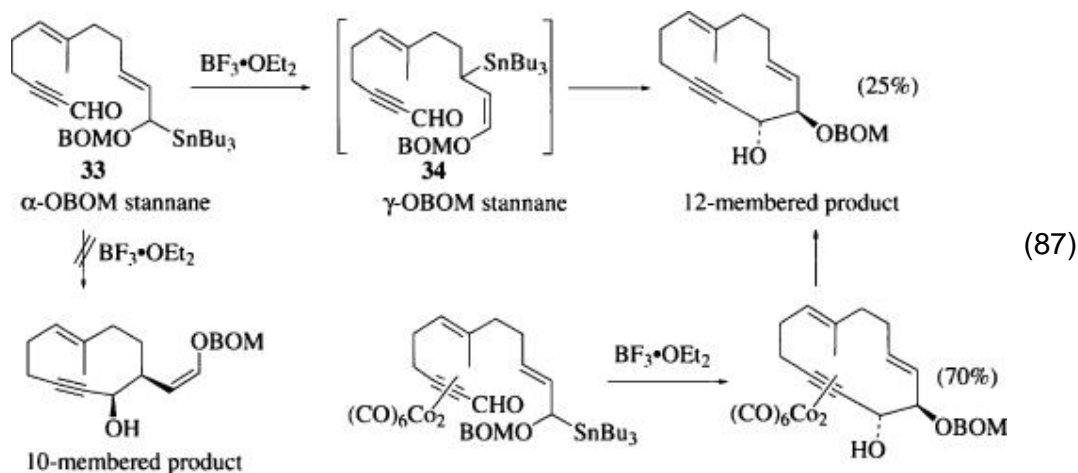


#### 3.8.1.1.2. Lewis Acid Promoted Reactions

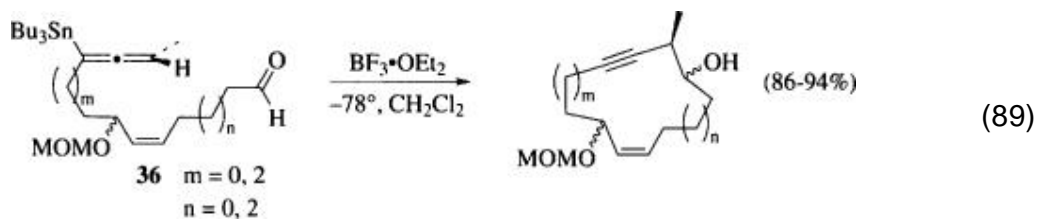
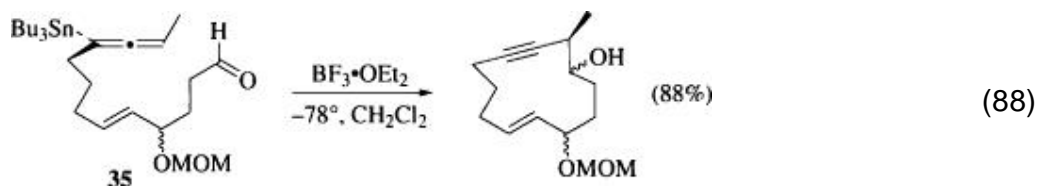
An intramolecular  $\alpha$ -(alkoxy)allylstannane-aldehyde addition yielding a 14-membered carbocycle is illustrated in Eq. 86. (102) The three steps leading to the cyclization precursor **32** from the aldehyde **31** are mild, which allows the synthesis to proceed in high yield. Although heating the aldehyde gives no identifiable product, treatment of **32** with  $\text{BF}_3 \cdot \text{OEt}_2$  at  $-78^\circ$  in  $\text{CH}_2\text{Cl}_2$  at high dilution affords the 14-membered carbocycle in 88% yield with the *cis* isomer as the major component of a 95:5 mixture. An enantioselective version of this macrocyclization was later reported. (103) The macrocycle was converted into a naturally occurring cembrane lactone.



The success of the macrocyclization depends on the structure of the precursor and the size of the ring. From an attempt to prepare a 10-membered carbocycle by this strategy, an unexpected 12-membered ring was isolated (Eq. 87). A 1,3-migration of the tributyltin group occurs from the initial  $\alpha$ -(alkoxy)allylstannane **33** to produce a  $\gamma$ -(alkoxy)allylstannane **34**, which undergoes subsequent addition to the aldehyde to afford the 12-membered cycle. (87, 104) The yield of the 12-membered ring is improved by changing the geometry of the acetylene moiety using a cobalt complex.



The cyclizations of allenylstannane aldehydes **35** and **36** have also been studied (Eqs. 88 and 89). (105) Stannanes **35** and **36** cyclize smoothly in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$  to afford 12- and 14-membered carbocycles in high yield. In each case, a nearly 1:1 mixture of syn and anti adducts is obtained.

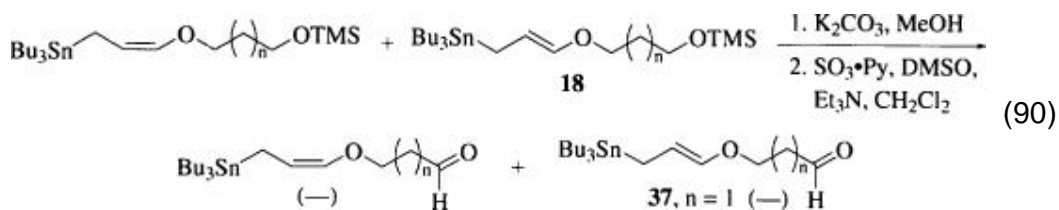




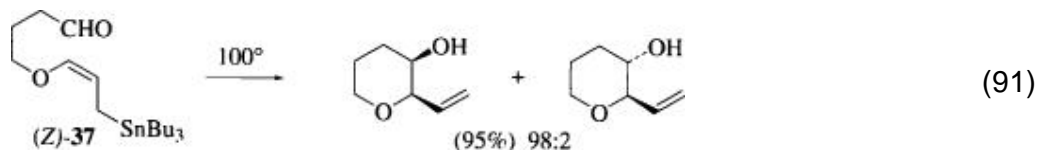
The requirement for the union of the allyl- or allenylstannane moiety with the aldehyde carbonyl carbon depends on the proper alignment of the two  $sp^2$  carbons. The connecting chain has a direct influence on the alignment of the reacting carbons. It has been observed that the intramolecular reaction works well for one substrate but not another due to a change in chain length and/or functional groups on the chain. Therefore the intramolecular allylstannane addition to aldehydes is not a general method for the formation of macrocycles.

### 3.8.1.2. Reactions Forming Cyclic Ethers

The cyclization of  $\alpha$ -(alkoxy)allylstannanyl aldehydes has been studied. (74, 94) The cyclization precursors are prepared from the corresponding TMS ethers (Eq. 90). The  $\gamma$ -(alkoxy)allylstannane function is stable under the conditions of TMS ether removal and oxidation of the resulting alcohol to the aldehyde.

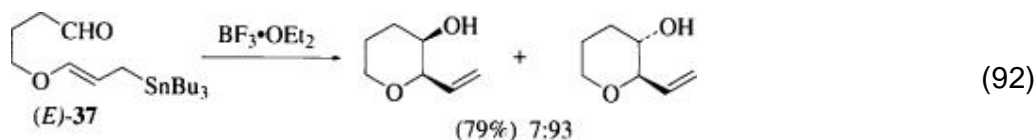


The thermal and Lewis acid promoted cyclizations of allylstannane aldehydes (*Z*)- and (*E*)-**37** has been studied (Eq. 91). (85) The formation of five- and six-membered rings can be achieved through either thermal or Lewis acid promoted intramolecular additions. The formation of a seven-membered ring can only be achieved in high yield through Lewis acid and protic acid promoted reactions. In general, under thermal conditions the *Z* stannane favors formation of the *cis* adducts and the *E* stannane favors formation of the *trans* isomer.



This trend is consistent with the cyclic transition structure proposed for

additions of allylstannanes to aldehydes under thermal conditions. However, the anti products are preferentially produced in the Lewis acid promoted reactions from both Z and E stannanes (Eq. 92). This relationship is explained through a transition structure where both the aldehyde-Lewis acid complex moiety and the allylstannane portion of the substrate assume pseudo-equatorial positions.

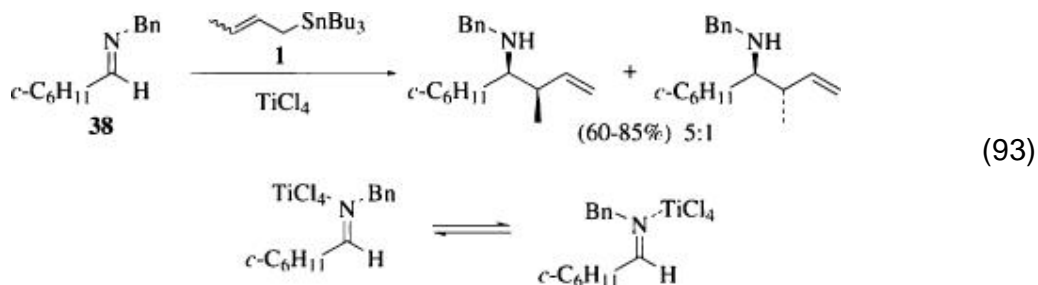


Intramolecular addition of allylstannanes to aldehydes is an efficient method for synthesizing 5–7 membered cyclic ethers. The most desirable characteristic of the reaction is the simultaneous production of both the 2-vinyl and 3-hydroxy substituents on the resulting cyclic ether, allowing for an iteration of the same reaction to produce a polycyclic ether.

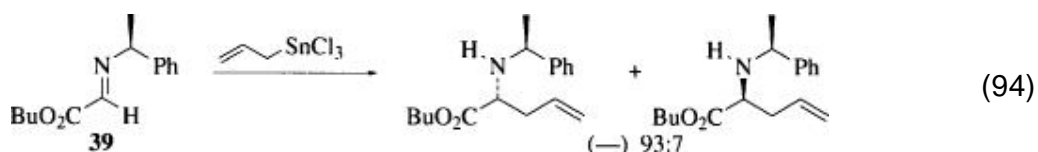
### 3.9. Reactions of Simple Allyl and 2-Butenylstannane Reagents with Imines

#### 3.9.1.1.1. Reactions Promoted by Lewis Acids

The addition of allylstannanes to imines can be promoted by Lewis acids. (106, 107) Imines are less reactive than aldehydes under the same conditions. The syn isomer is obtained as the major component of a ca. 5:1 mixture when 2-butenylstannane **1** reacts with imine **38** (Eq. 93). If  $\text{TiCl}_4$  is used as the Lewis acid, the ratio of products depends on the time of pre-mixing the imine and the Lewis acid. (106) The longer the pre-mix time, the higher the syn:anti ratio observed. This effect may have its origin in the configuration of the aldimine- $\text{TiCl}_4$  complex. Similar results are obtained in the  $\text{BF}_3$  promoted addition of crotyltributylstannane to imines. (107) An antiperiplanar transition structure similar to that suggested for the reactions with aldehydes also accounts for the stereochemical course of the imine reactions. However, unlike aldehydes, no reaction occurs when imines and the stannane reagents are heated under high pressure.

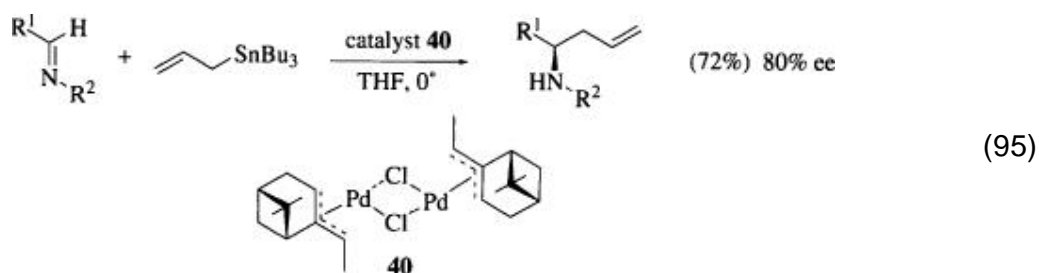


Additions to more reactive imines using allyltrichlorostannane are reported. (21) A useful level of stereoselectivity is observed when imine **39** (prepared from butyl glyoxalate and (*S*)- $\alpha$ -methylbenzylamine) is subjected to the reaction (Eq. 94). The products are the amino esters in a ratio of 93:7. This stereoselectivity is complementary to the reaction with allyl-9-BBN, which gives the opposite selectivity in a ratio of 10:90. (108)



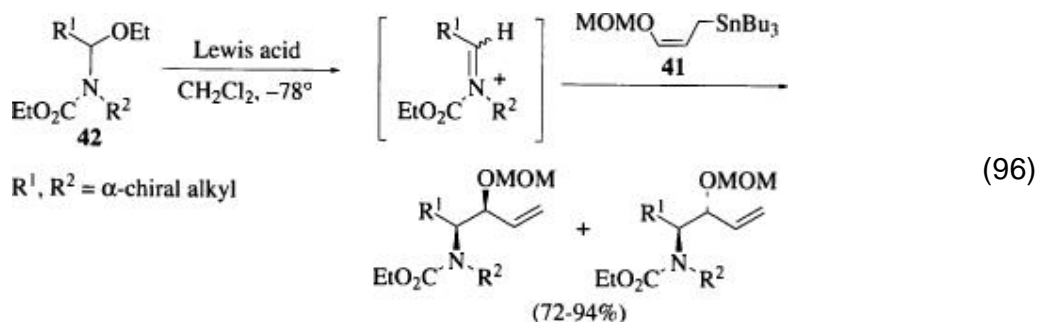
#### 3.9.1.1.2. Reactions Promoted by a Palladium Catalyst

Imines undergo the allylation reaction in the presence of palladium catalysts to afford homoallylamines in high yields. (109, 110) Allylation of imines occurs preferentially in the presence of aldehydes. Mechanistic studies reveal that a bis- $\pi$ -allylpalladium complex is a reactive intermediate for this allylation reaction. Although ordinary  $\pi$ -allylpalladium complexes, such as  $\pi$ -allyl-PdX (X = OAc or halides), act as electrophiles, the bis- $\pi$ -allylpalladium complex reacts with imines as a nucleophile. The lone pair of electrons on the nitrogen atom of imines associates with the palladium atom more strongly than those of the aldehyde oxygen atom, which explains why imines are more reactive under these conditions. (109, 110) By proper choice of the allyl ligands, one of the allyl groups is selectively transferred to the imine. A chiral allyl group serves as a non-transferable ligand. The chiral  $\pi$ -allylpalladium complex **40** induces asymmetric allylations of imines by the allylstannane with up to 80% ee (Eq. 95). (111)

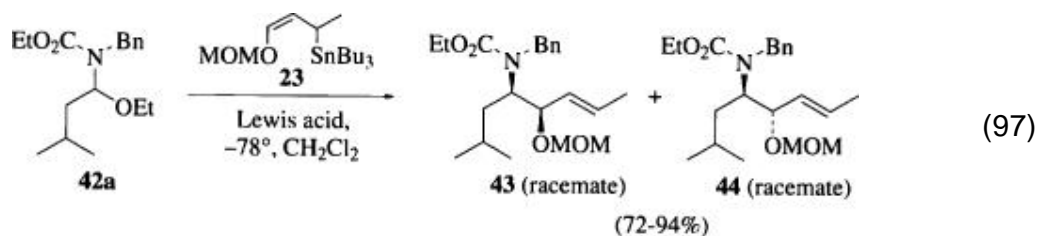


### 3.9.1.1.3. Reactions of $\gamma$ -(Alkoxy)allylstannanes with Iminium Ions

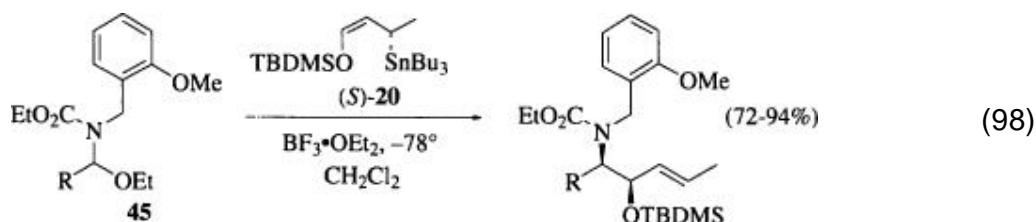
The addition of  $\gamma$ -MOM allylic stannane **41** to several *N*-acyliminium intermediates is described (Eq. 96). (112) The acyliminium ions are generated from the corresponding  $\alpha$ -ethoxy carbamates **42** in the presence of a Lewis acid. High yields of the amino alcohol derivatives are obtained from the reactions of  $\gamma$ -MOM allylic stannane **41** and the acyliminium ions. The Lewis acids  $\text{TiCl}_4$  and  $\text{BF}_3 \cdot \text{OEt}_2$  are effective. Formation of the acyliminium ion under these conditions is confirmed by low temperature NMR spectroscopy. (112)



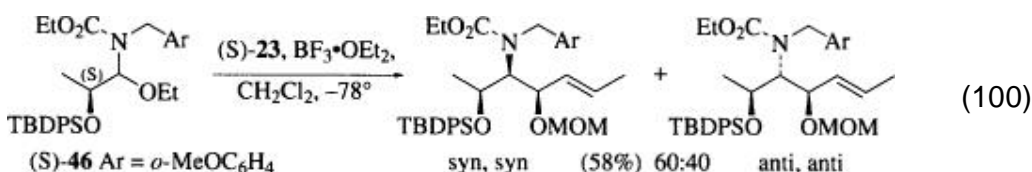
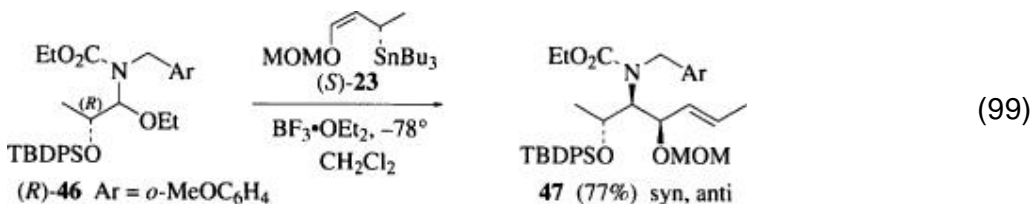
Addition of the chiral  $\gamma$ -(alkoxy)allylstannanes **20** and **23** to iminium ions is also reported (Eq. 97). (113) Addition of the racemic  $\gamma$ -oxygenated allylic stannanes (*Z*)-**23** to the *N*-acyliminium precursor **42a**, derived from isovaleraldehyde, proceeds in high yield to afford a mixture of syn and anti isomers **43** and **44**.



The reaction between the *o*-methoxybenzyl derivative **45** and the enantioenriched  $\gamma$ -(silyloxy)allylic stannane (*S*)-**20** has also been examined (Eq. 98). The syn adduct predominates over the anti adduct by >95:5.



The matched/mismatched characteristics of the addition process have been examined with the allylic stannane (*S*)-**23** and the *N*-(*o*-methoxybenzyl)carbamates **46** derived from (*R*)- and (*S*)-lactic aldehyde (Eqs. 99 and 100). Similar to analogous additions to aldehydes, the R/S combination is the matched pairing and affords the syn, anti adduct **47** as the exclusive product (Eq. 99). The S/S combination leads to a 60:40 mixture of the syn, syn and anti, syn adducts (Eq. 100).



The observed diastereoselectivity is consistent with a preferred antiperiplanar acyclic transition structure. The reason for the unprecedented enhanced diastereoselectivity of the *o*-methoxybenzyl derivatives is unclear.

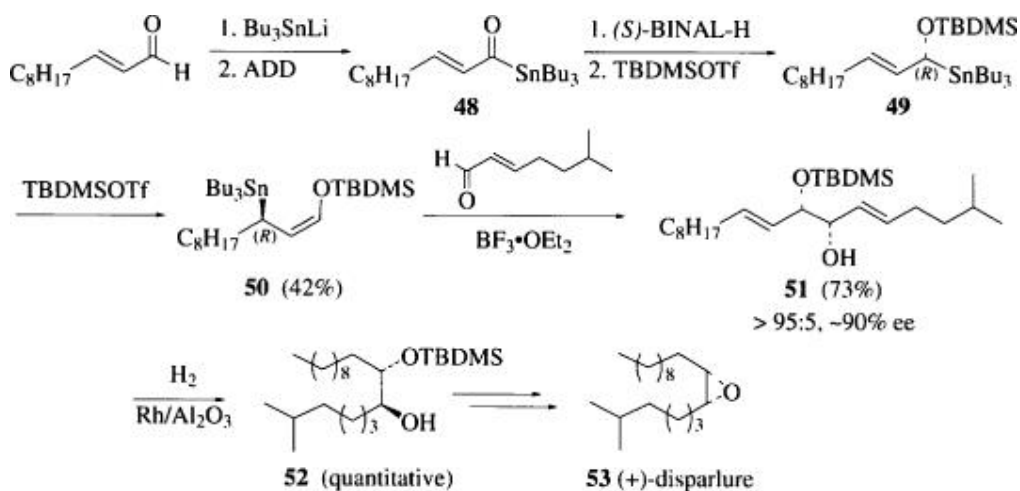
## 4. Applications to Synthesis

A few representative examples of applications of stannane chemistry in natural product syntheses are presented here to show the diversity of this useful reaction. No effort was made to provide an exhaustive coverage of all published applications. The following total syntheses were chosen because of the relative importance of the stannane reagents in the overall processes.

### 4.1. (+)-Disparlure

The sex attractant of the female gypsy moth, (+)-disparlure (**53**), has been the object of numerous synthetic investigations. The earliest approaches employ chiral pool starting materials with diol functionality of appropriate chirality. More recently, the Sharpless asymmetric epoxidation and dihydroxylation have been employed to introduce the requisite epoxide stereocenters. The use of  $\gamma$ -(alkoxy)allylstannane chemistry combines chain elongation and introduction of the chiral diol centers in a single step (Scheme 1). (114) The  $\alpha$ -(silyloxy)stannane reagent provides the desired configuration at the two centers. Thus, addition of  $\text{Bu}_3\text{SnLi}$  to (*E*)-2-undecenal followed by in situ oxidation affords the acylstannane **48**. Reduction with (*S*)-BINAL-H and in situ treatment with TBSOTf yields the  $R$   $\gamma$ -(silyloxy)stannane **50** via the  $\alpha$ -isomer **49** in 42% overall yield. Stannane **50** is readily purified by column chromatography on silica gel. Addition of **50** to 6-methyl-2-heptenal in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$  affords the syn adduct **51** in 73% yield and >90% ee. Less than 5% of the anti diastereomer is formed in the addition. Hydrogenation of **51** over  $\text{Rh}/\text{Al}_2\text{O}_3$  affords the tetrahydro adduct **52** quantitatively. The tosylate derivative of **52** upon treatment with TBAF in THF smoothly cyclizes to (+)-disparlure (**53**) in high yield.

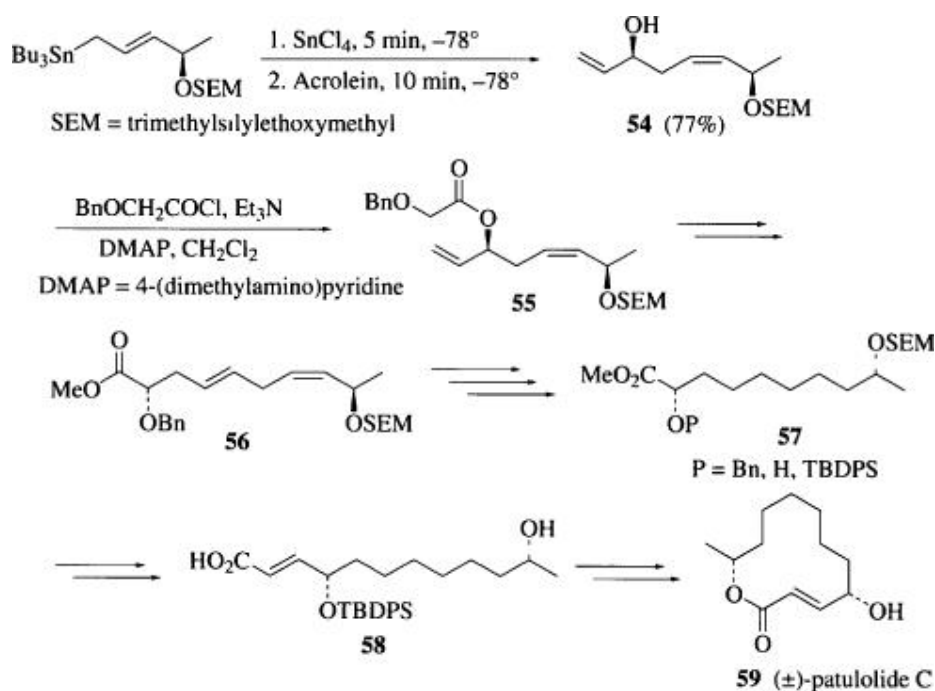
Scheme 1.



### 4.2. ( $\pm$ )-Patulolide C

A combination of  $\delta$ -(alkoxy)allylstannane chemistry and a sigmatropic rearrangement can be used to stereoselectively prepare compounds with distant stereogenic centers (Scheme 2). (115) As one stereogenic center is used to influence the introduction of the second, this approach can be used to synthesize racemic compounds diastereoselectively, as well as for the synthesis of enantiomerically enriched compounds. In the total synthesis of ( $\pm$ )-patulolide C (59), the relative configuration of 1,8-stereogenic centers is controlled by the tin(IV) chloride promoted reaction of acrolein with (4-hydroxy-pent-2-enyl)tributylstannane (trimethylsilyl)ethoxymethyl ether, which proceeds with >97:3 1,5-asymmetric induction in favor of the desired syn isomer 54. An Ireland-Claisen rearrangement is carried out with the ester 55, which goes through a Z silylketene acetal intermediate and rearranges through a chair-like transition structure giving the 2,9-anti configuration in ester 56. Diimide reduction of 56 followed by protecting group transformation affords the saturated ester 57, which is then elaborated into hydroxy acid 58. Acid 58 is then cyclized to ( $\pm$ )-patulolide C (59).

Scheme 2.



### 4.3. Spongistatin 1

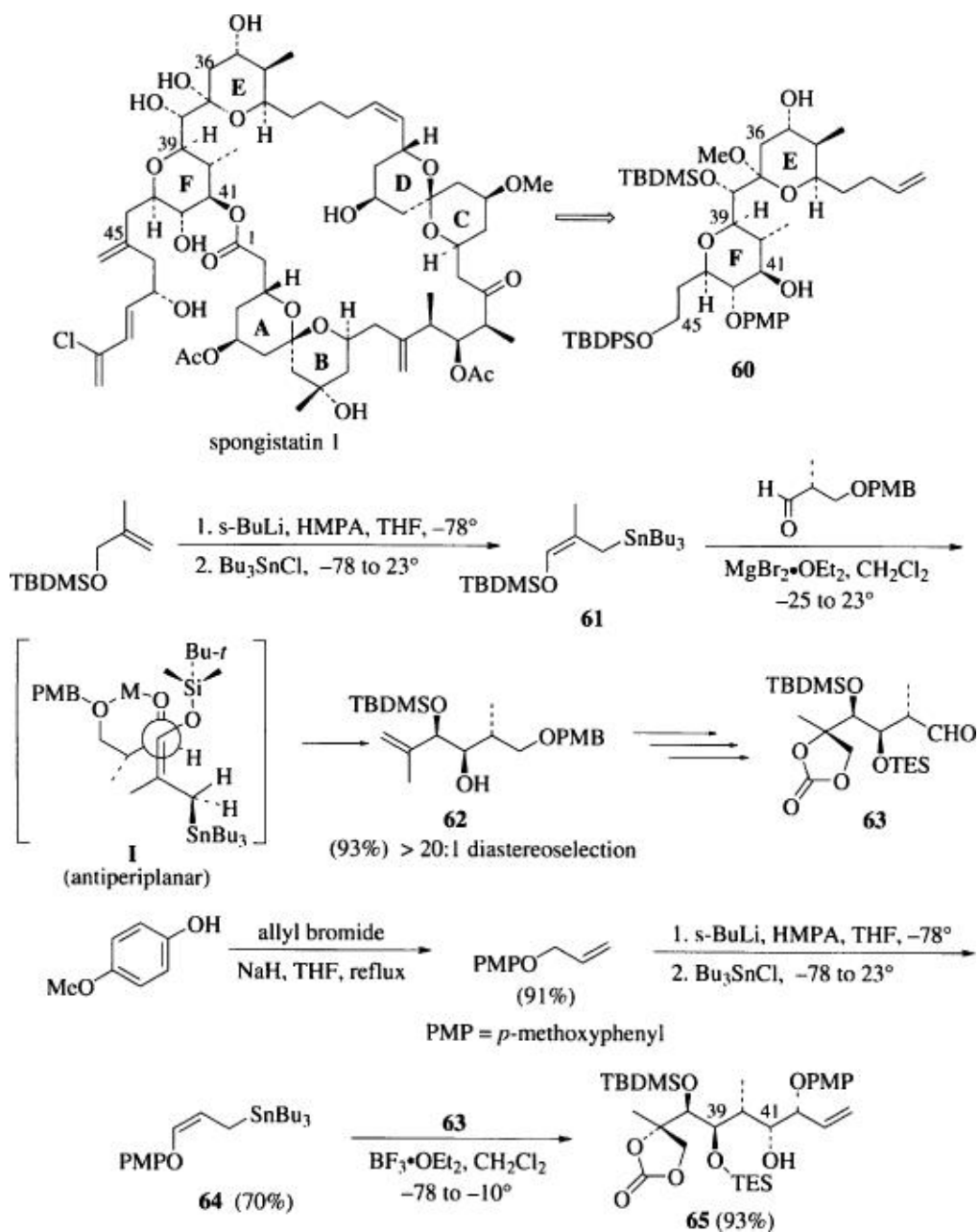
The efficiency and convenience of the applications of achiral  $\gamma$ -(alkoxy)allylstannanes are demonstrated in the diastereoselective synthesis of the C(29)-C(45) subunit 60 of spongistatin 1 (Scheme 3). (116) Spongistatin 1, one of the most active members of the spongipyran family, is a complex macrocyclic structure with six highly oxygenated heterocycles. The synthesis proceeds in 19 steps from chiral aldehyde 8, and features highly diastereoselective  $\alpha$ -alkoxyallylation reactions using  $\gamma$ -alkoxy substituted

allylstannanes **61** and **64**. Metallation of *tert*-butyldimethylsilyl methallyl ether followed by addition of Bu<sub>3</sub>SnCl affords the β -methyl- γ -(alkoxy)allylstannane **61** (64%). Chelation controlled addition of **61** to aldehyde (*R*)-**8** (MgBr<sub>2</sub>·Et<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, – 25 to 23°) provides the anticipated homoallylic alcohol **62** in 93% yield with greater than 20:1 stereoselectivity.

It is suggested that the antiperiplanar transition structure **I** is preferred in this case compared to synclinal transition structures because it can better accommodate the large *tert*-butyl substituent of γ -(alkoxy)allylstannane **61**. The homoallylic alcohol **62** is transformed into aldehyde **63** using standard protocols. γ -(Alkoxy)allylstannane **64**, needed for homologation of **63**, is generated by alkylation of *p*-methoxyphenol with allyl bromide followed by metalation with *s*-BuLi and addition of Bu<sub>3</sub>SnCl. The treatment of aldehyde **63** with allylstannane reagent **64** and BF<sub>3</sub>·Et<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub> at –78° gives the desired alcohol **63** in 93% yield with >20:1 diastereoselectivity. The configuration of product **65** is consistent with 1,2- and 1,3-merged asymmetric induction. With these efficient steps, the **E-F** bis-pyran portion of spongistatin 1 was prepared successfully.

**Scheme 3.**



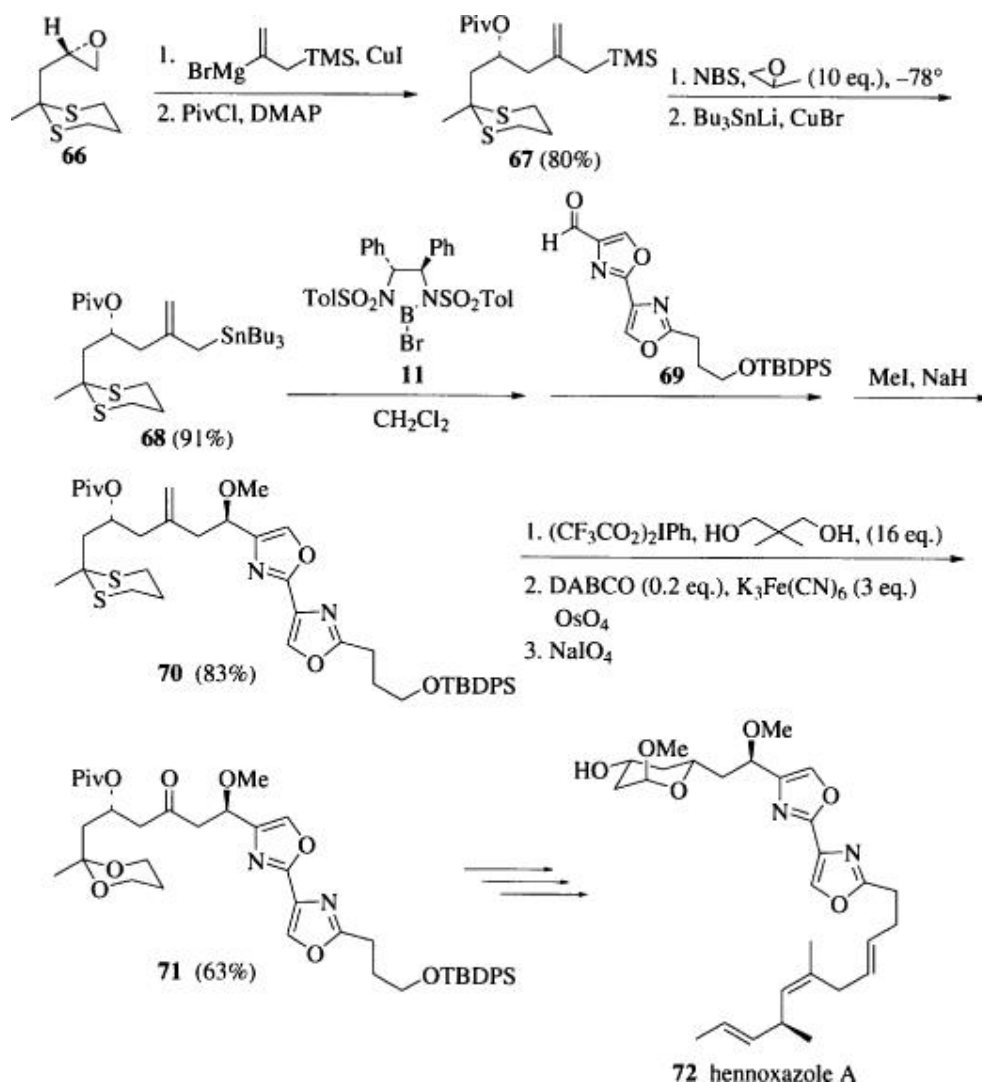


#### 4.4. Hennoxazole A

Efficient application of a highly functionalized allylstannane using chiral controller **11** is demonstrated in the total synthesis of hennoxazole A (**72**). (**117**) Compound **72** is isolated from the sponge *polyfibrospongia* and displays potency against herpes simplex virus type 1. The application of the mild asymmetric allylation strategy developed on the basis of stannane chemistry is employed to construct the C1-C17 portion of the target compound (Scheme 4). Stannane **68** is prepared via copper-catalyzed Grignard addition starting from 2-bromo-3-trimethylsilylpropene and epoxide **66**. The superior reactivity of allylstannane **68** is required as the silane **67** fails to undergo transmetalation

with the bromoborane **11**. Formation of the protected homoallylic alcohol (*R*)-**70** by transmetalation of optically pure stannane **68** with bromoborane (*R,R*)-**11** yields an intermediate borane for condensation with aldehyde **69**. Stereocontrol (10.5:1 d.s.) is induced from the 1,2-diphenylethane sulfonamide auxiliary. The final target is obtained in six more steps consisting of mostly functional group transformations, including oxidation of intermediate product **70** to ketone **71**.

Scheme 4.

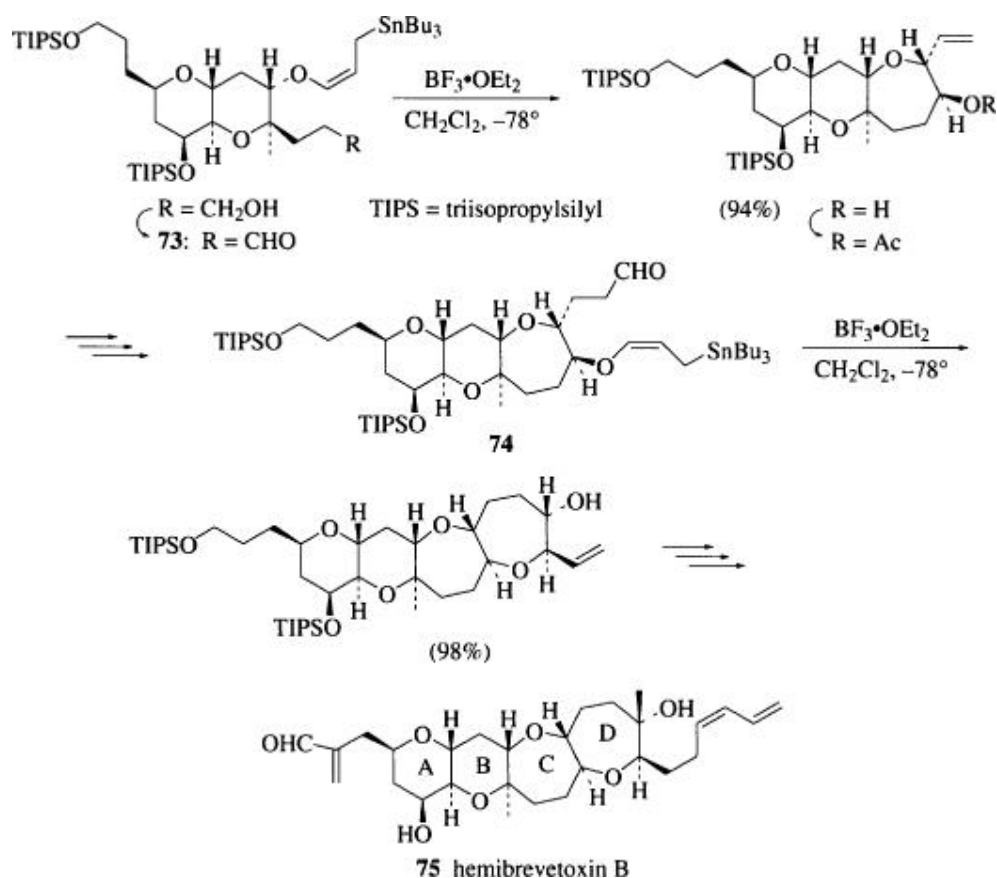


#### 4.5. Hemibrevetoxin B

The most extensive application of allylstannane chemistry in an intramolecular setting is shown in the total synthesis of hemibrevetoxin B (**75**). The efficiency of the intramolecular reaction of a  $\gamma$ -alkoxystannane with aldehydes as a tool for the synthesis of a polycyclic ether was documented in this synthesis. (118) The total synthesis is accomplished with high stereoselectivity in 56 steps and

0.75% overall yield from mannose. The efficiency of the synthesis exceeds other synthetic routes by factors of 15–20. Two key transformations in the synthesis, shown in [Scheme 5](#), involve intramolecular additions of allylstannanes to aldehydes (**73** and **74**) in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$ . As discussed earlier, both the aldehyde-Lewis acid complex and the allylstannane portion of the substrate assume pseudoequatorial positions in the cyclization process affording the trans isomer stereoselectively.

**Scheme 5.**

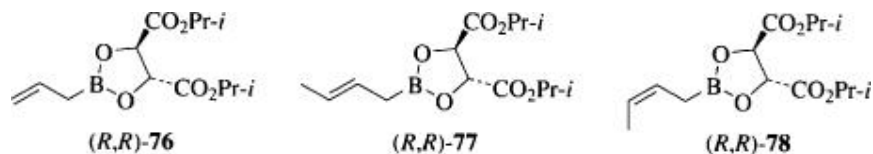


## 5. Comparison with Other Methods

The versatility of stannane reagents is illustrated in this chapter. The fact that an oxygen atom can be incorporated at various positions in allylstannane reagents improves their utility in natural product synthesis. The ready exchange of stannane with other metals before addition to an electrophilic carbon further increases the applications of stannane reagents. As a group, stannane reagents provide versatile tools for the synthetic chemist. For certain transformations, however, other reagents may have superior or complementary properties. For example, in the presence of a Lewis acid, 2-butenylstannanes form 1,2-syn adducts in addition reactions with aldehydes. In a substrate-controlled reaction, three contiguous stereocenters can be produced with 2-butenylstannane reagents. The triads with 1,2-syn, 2,3-syn or 1,2-syn, 2,3-anti configuration can be obtained depending on the choice of chelating or non-chelating Lewis acid. To obtain 1,2-anti configuration from stannane reagents, transmetalation with a chelating Lewis acid, such as SnCl<sub>4</sub>, TiCl<sub>4</sub>, or InCl<sub>3</sub>, is required before the addition reaction takes place. In this regard, other allylmetal reagents, such as allylboranes, are complementary for the synthesis of 1,2-anti adducts. The reagent-controlled addition of an allyl or a crotyl group to an aldehyde by a tartrate-derived boronate reagent or a diisopinocampheylborane in particular has attracted wide-spread applications. Many other allylic metal reagents have been developed. A brief discussion of allylsilane, allylzinc, allyllithium, allylchromium, and allyltitanium reagents follows the discussion of allylboron species.

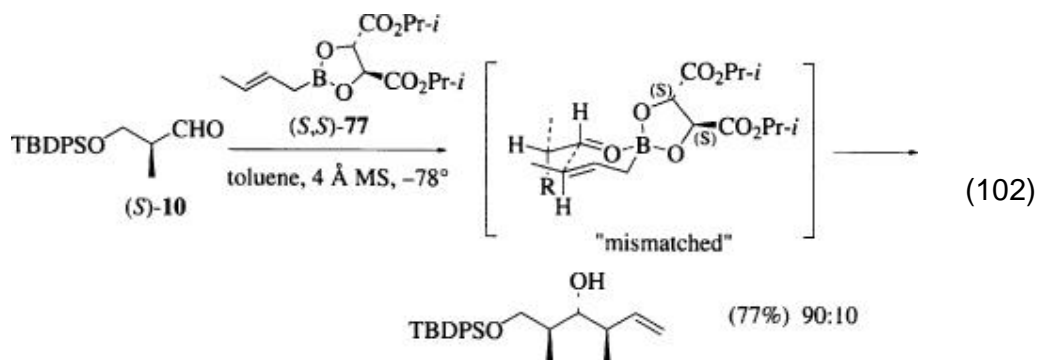
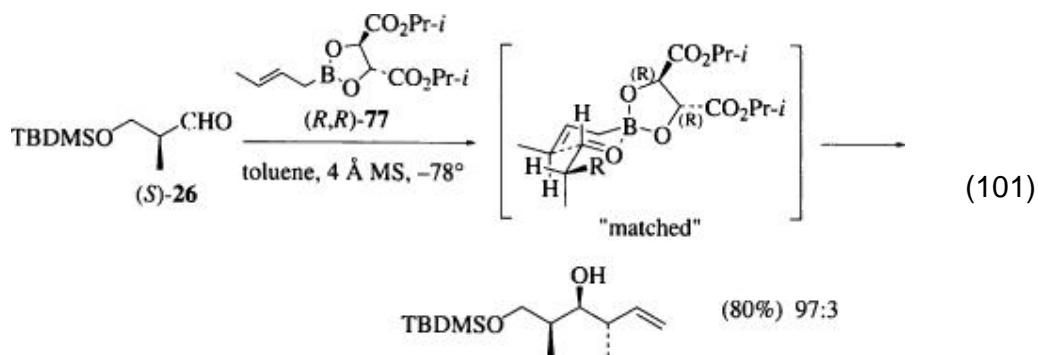
### 5.1. Tartrate Derived Allylboronate Reagents

Tartrate derived chiral allyl- and crotylboronate reagents have been developed. (9, 119) These reagents have been used in the synthesis of complex natural products. (114-121) In comparison to chiral (alkoxy)allylstannanes, chiral boronates are more convenient to prepare from commercially available materials. Allylboronate **76** is prepared from the reaction of allylmagnesium bromide with trimethylborate followed by esterification with diisopropyl tartrate (DIPT) in the presence of MgSO<sub>4</sub>. (120) In analogous fashion, the E and Z crotylboronates **77** and **78** are prepared in high isomeric purity (>98%) from (E)- and (Z)-2-butene by way of the (E)- and (Z)-crotylpotassiums. (121)



In Lewis acid mediated additions, allylstannanes add to aldehydes through an

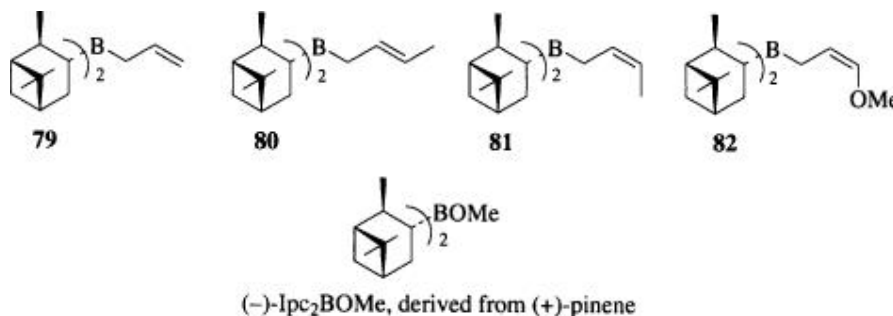
open transition state. In contrast, allylboronate reagents add to aldehydes through a cyclic six-membered, chair-like transition state. These reagents give high levels of asymmetric induction (83–98% ee) with metal carbonyl complexed unsaturated aldehydes. (122-124) The complementary properties to allylstannanes are shown in the following equations. Crotylboronate reagent (*R,R*)-**77** adds to aldehydes yielding 1,2-anti products in high stereoselectivity. The tartrate-derived crotylboronate reagents are most useful in the context of double asymmetric reactions with chiral aldehydes. (125, 126) Equations 101, 102 demonstrate the utility of (*E*)-**77** and (*Z*)-**78** in the synthesis of dipropionate adducts. The TBDMS-protected  $S\alpha$ -methyl- $\beta$ -alkoxy aldehyde **26** reacts with the crotylboronate (*R,R*)-(*E*)-**77** to give the syn, anti dipropionate as the major adduct with high diastereoselectivity (97:3). The stereochemical outcome of this reaction is rationalized by the matched transition structure, where C - C bond formation occurs by addition of the crotylboronate anti to the TBDMSOCH<sub>2</sub>-substituent of the Felkin-Anh rotamer of the aldehyde. Both the crotyl-boronate reagent and the  $\alpha$ -chiral aldehyde prefer this pathway. The anti, anti-dipropionate is obtained with useful selectivity (90:10) from the reaction of the aldehyde (*S*)-**10** with (*S,S*)-(*E*)-**77**. The stereochemical outcome of this mismatched double asymmetric reaction is depicted in the transition structure where C - C bond formation occurs with the crotylboronate adding to the anti-Felkin-Anh rotamer of aldehyde (*S*)-**10**. The reagent is dominant in the stereochemical outcome.



Although these anti triads can also be prepared using allylstannane chemistry, a more elaborate procedure needs to be followed. On the other hand, allylstannanes are excellent reagents for preparing syn triads.

## 5.2. Diisopinocampheyl-, Allyl-, and Crotylborane Reagents

A family of highly enantioselective chiral allylborane reagents derived from naturally occurring pinene has been developed. (127, 128) A list of literature references that documents the use of these pinene-derived reagents in natural product synthesis from 1985–1993 appears in a review. (127, 128) These allylborane reagents add to aldehydes through a six-membered, cyclic transition state. While allylstannanes are relatively insensitive to moisture and air, these borane reagents must be used under an inert atmosphere (nitrogen or argon).



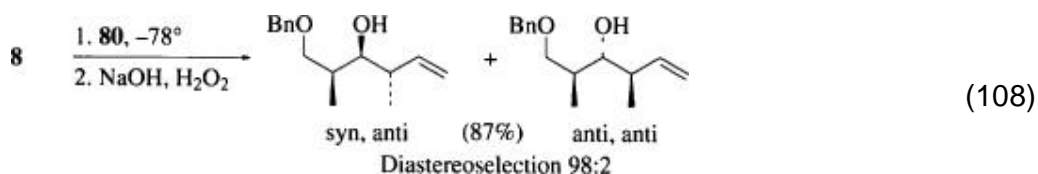
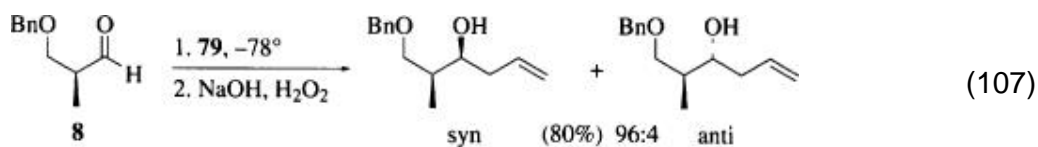
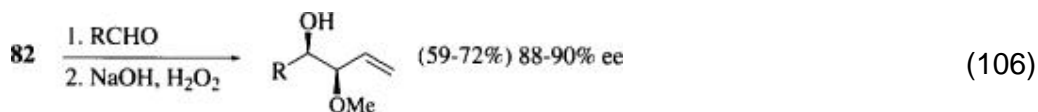
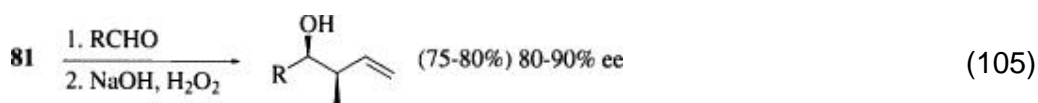
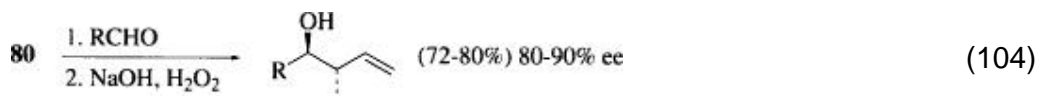
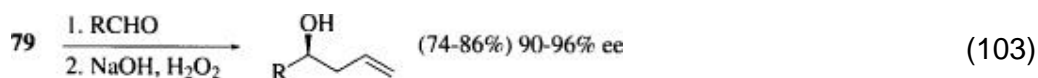
Reagents **79–82** are synthesized starting from commercially available  $\beta$ -methoxy-diisopinocampheylborane, (-)-lpc<sub>2</sub>BOMe, or (+)-lpc<sub>2</sub>BOMe. The (lpc)<sub>2</sub>BAlI reagent **79** is prepared by reaction of (-)-lpc<sub>2</sub>BOMe with allylmagnesium bromide followed by removal of the Mg<sup>2+</sup> salts by filtration. (129, 130) Removal of the Mg<sup>2+</sup> salts dramatically increases the reactivity of **79** with aldehydes, making it possible to perform these reactions at -100° with substantially improved enantioselectivity compared to reactions performed at -78°.

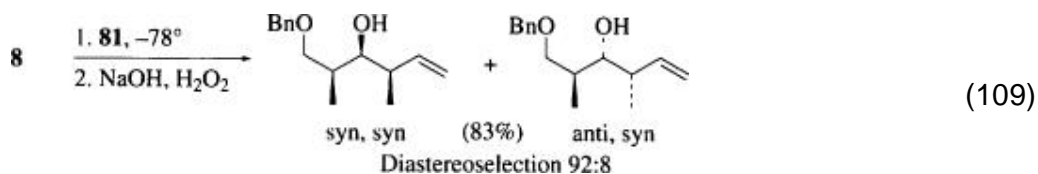
Reagents **80** and **81** are prepared from *trans*- and *cis*-2-butene, (131) respectively, through a modification of the deprotonation conditions developed by Schlosser. (132) Addition of (-)-lpc<sub>2</sub>BOMe to the E and Z crotylpotassium reagents, respectively, generates the corresponding allylborate complexes, which upon treatment with BF<sub>3</sub>·OEt<sub>2</sub> give the crotylboranes **80** and **81**.

Reagent **82** is prepared from allyl methyl ether via deprotonation with *sec*-butyllithium and subsequent treatment with (-)-lpc<sub>2</sub>BOMe and then BF<sub>3</sub>·OEt<sub>2</sub>. (133) For best results, these reagents should be prepared just prior

to use because **80**, **81**, and **82** are configurationally unstable at temperatures above  $-78^\circ$ .

These reagents react in a highly diastereo- and enantioselective manner with achiral aldehydes (Eqs 103–106). (129-131, 134) The double asymmetric reactions of reagents **79–81** with chiral aldehydes generally result in selective formation of the product predicted from reagent control of asymmetric induction. Results of the reactions of aldehyde **8** and reagents **79–81** are summarized in Eqs. 103–106. (135-137) Compared to allylstannane reagents, these borane reagents are more sensitive to air and moisture and must be freshly prepared before each reaction.





### 5.3. Allyllithium Reagents

The reactions of allylic lithium reagents with ketones or aldehydes have been used extensively to prepare homoallylic alcohols. (138) The corresponding 2-butenyllithium reagents are configurationally unstable, existing as a mixture of rapidly equilibrating E and Z isomers. (139) The utility of the 2-butenyllithium reagents increases when a heteroatom or heterocycle-stabilized allylic anion is employed. The control of  $\alpha$ - vs.  $\gamma$ -substitution in allyl anions depends upon a number of conditions, including the nature of the stabilizing group, charge delocalization, steric effects, solvation, and the counterion. The heteroatom or heterocycle-stabilized reagents show their greatest utility after transmetalation to another metal, such as tin. (140) The advantages of the allylic lithium reagents include their easy availability and their disadvantages are their strong basicity and their lack of stereocontrol in reactions with aldehydes.

### 5.4. Allylsilanes

The reaction of allylsilanes with various electrophiles is one of the most studied methods of carbon-carbon bond formation. (141-144) One of the advantages of allylic silicon reagents when compared to other reagents is their stability. Allylsilanes are insensitive to water and have low toxicity. They are readily handled and can be stored for long periods of time without special precautions; they are considerably less reactive than allylstannanes. For example, transmetalation to an allylborane from an allylsilane failed while a corresponding allylstannane succeeded. (117) If the electrophile is not reactive, transmetalation is required to convert the stable allylsilane into a more reactive allylic metal reagent, such as an allylstannane. (117)

One of the more important developments in allylation reactions is the catalytic enantioselective variant. Examples of catalytic enantioselective allylation of aldehydes using allylsilanes have been reported. (145) The chiral (acyloxy)borane (CAB) catalyst is used to produce the desired homoallylic alcohols in moderate to good yields when substituted allylsilanes are employed. The reaction gives best results when  $\beta$ -alkyl substituted allylsilanes are used in conjunction with aromatic aldehydes. Aliphatic aldehydes afford the homoallylic alcohols in 20–36% yield, although with a good enantioselectivity (85–90%). A BINOL-titanium complex is also employed as a



catalyst in the addition of allylsilanes to aldehydes. (146) This catalyst affords homoallylic alcohols in moderate diastereo- and enantioselectivity with 2-butenylsilane and methyl glyoxylate.

### 5.5. Allylchromium Reagents

The chromium(II) mediated reaction of 2-butenyl bromide with aldehydes affords the anti homoallylic alcohol in high diastereoselectivity regardless of the geometry of the starting allylic bromide. (147, 148) The allylchromium reagents are complementary to allylstannane reagents in that they generate 1,2-anti stereochemistry. Chromium mediated reactions of allylic phosphates with aldehydes have also been developed. (149) The reactions of  $\gamma$ -disubstituted and  $\beta$ ,  $\gamma$ -disubstituted allylic phosphates with aldehydes mediated by chromium proceed with good to excellent diastereoselectivity. The geometry of the starting allylic phosphate reagent determines the stereochemical outcome of the reaction. An efficient catalytic enantioselective employment of allylchromium reagents has yet to be developed. (150, 151) Compared to allylstannanes, allylchromium reagents have rather limited applications in synthesis.

### 5.6. Allylzinc Reagents

The allylation of aldehydes with allylic zinc reagents proceeds in moderate to high yield and high regioselectivity to afford homoallylic alcohols. (152) However, the 2-butenylzinc reagents are configurationally unstable, providing a mixture of syn and anti homoallylic alcohols upon reaction with aldehydes.

The addition of allylzinc reagents to electrophiles is known to be a reversible process. An application of masked allylic zinc reagents for highly diastereoselective allylation takes advantage of this reversible process. (153, 154) Upon formation of a zinc alkoxide, a sterically hindered tertiary homoallylic alcohol undergoes fragmentation to generate an allylic zinc reagent that subsequently undergoes reaction with an electrophile. High yields and diastereoselectivities have been reported for the generation of 1,2-anti homoallylic alcohols in this manner.

Although simple dialkylzinc reagents give excellent enantioselectivity in the addition to aldehydes in the presence of an amino alcohol, (155) allylations of aldehydes are better conducted with allylstannane reagents.

### 5.7. Allylindium Reagents

The addition of 2-butenylindium reagents to aldehydes has been shown to give homoallylic alcohols in high yields albeit low selectivity. Allylindium reagents can be prepared by reductive metalation of allylic halides or phosphates with indium metal, or by transmetalation of allylstannanes with indium trichloride. (83, 156) Indium reagents are inert to water and are used in aqueous solutions. For the allylic indium reagents generated by reductive metalation, the

formation of allylindium(I), rather than allylindium(III), is proposed. (157) The allylindium reagents generated from transmetalation with allylstannanes derive from an  $S_E\phi$  attack by  $\text{InCl}_3$  on the allylstannane. (83) Allylindium reagents alone are incomparable to allylstannane reagents in terms of stereoselectivity and versatility. Reactions performed in water produce homoallylic alcohols in high yield albeit low stereoselectivity. (158) However, through transmetalation with the chiral  $\alpha$ -(alkoxy)allylstannane, the transient allylindium reagents react with aldehydes with excellent diastereoselectivity. (83)

## 6. Experimental Conditions

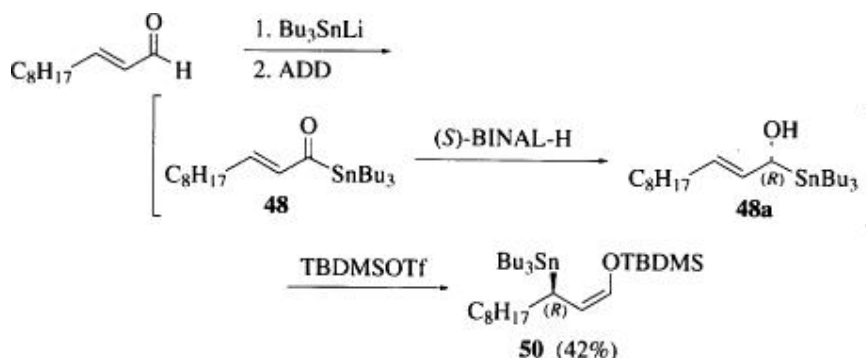
The intermolecular addition of  $\alpha$ -(alkoxy)allylstannanes to aldehydes without a catalyst or promoter requires heating the mixture at 100–130°. In the presence of one equivalent of a Lewis acid, such as  $\text{BF}_3 \cdot \text{OEt}_2$ , the addition proceeds at  $-78^\circ$ . In certain cases where a chelation-controlled addition is required,  $\text{SnCl}_4$  is used as the desired Lewis acid and the temperature should be controlled at around  $-90^\circ$ . In general, anhydrous conditions and an inert atmosphere are required for these reactions. However, the whole operation is relatively simple and does not require extreme measures in drying the reagents or apparatus. Allyltributylstannane is commercially available. Other simple alkyl-substituted allylstannanes can be prepared by known procedures using the corresponding allylic halide and tributyltin chloride.

*Caution! Volatile organotin compounds, such as trimethylallylstannane, are highly toxic. Tributylallylstannane is not volatile and therefore less hazardous. All reactions involving the use of organotin reagents should be conducted in a well-ventilated fume hood.*

The preparation of the optically enriched  $\alpha$ -(alkoxy)allylstannanes requires the preparation of a chiral reducing reagent and an acylstannane. The chiral reducing reagent BINAL-H gives the highest enantioselectivity. The protocol for preparing this reagent is well documented (see “[Experimental Procedures](#)”). The BINAL-H must be freshly prepared just before the acylstannane is ready for reduction due to the lability of the acylstannane. The resulting  $\alpha$ -(hydroxy)stannane is also labile and needs to be protected as its MOM, BOM, or TBDMS ether immediately after isolation. Therefore, planning ahead is key to the success of the preparation of the enantiomerically enriched  $\alpha$ -(alkoxy)allylstannanes, which can be stored in a refrigerator for weeks. Additions of  $\alpha$ -(alkoxy)allylstannanes to aldehydes usually proceed at  $-78^\circ$  with a full equivalent of  $\text{BF}_3 \cdot \text{OEt}_2$ .

The reaction conditions for the addition of allenylstannanes to aldehydes are similar to those described for allylstannanes. When  $\text{MgBr}_2 \cdot \text{OEt}_2$  is used as the Lewis acid promoter, the reactions are usually conducted at  $0^\circ$  due to the weaker acidity of  $\text{MgBr}_2$ .

## 7. Experimental Procedures



### 7.1.1.1. (Z)-(R)-1-(tert-Butyldimethylsilyloxy)-3-tri-n-butylstannyl-1-undecene (**50**) [Preparation of a Chiral $\gamma$ -(Silyloxy)allylstannane from an $\alpha$ , $\beta$ -Unsaturated Aldehyde] (114)

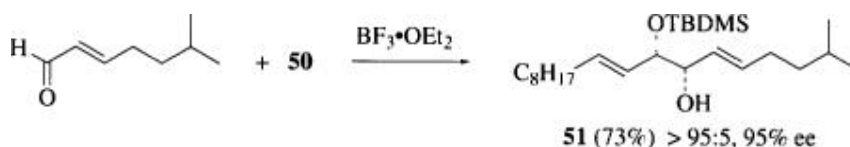
Diisopropylamine (1.67 mL, 11.9 mmol) in 75 mL of anhydrous THF was cooled to 0° and *n*-BuLi was added (2.5 M solution in hexane, 4.72 mL, 11.8 mmol), followed after 15 minutes by tributyltin hydride (3.17 mL, 11.8 mmol). The resulting yellow solution was stirred for 20 minutes. The solution was cooled to -78° and 2-undecenal (1.81 g, 10.8 mmol) was added, followed after 30 minutes by 1,1 $\phi$ -(azodicarbonyl)dipiperidine (ADD, 4.15 g, 16.5 mmol), and the resulting dark red reaction mixture was warmed to 0° and stirred for 1 hour. The reaction was then quenched with dilute aqueous NH<sub>4</sub>Cl solution and the mixture was extracted with Et<sub>2</sub>O. The organic extracts were combined, dried over MgSO<sub>4</sub>, and the solvent was removed under reduced pressure. Hexane was added to the orange residue and the solution was concentrated under reduced pressure to remove any traces of THF. Precipitating residual ADD with hexane purified the acyl stannane **48**. The solid was removed by vacuum filtration and the filtrate concentrated to provide the acyl stannane.

*Because of the lability of the acyl stannane it is important to have a freshly prepared solution of BINAL-H at -78° ready for the subsequent reduction. This is best achieved by starting the following procedure for BINAL-H just prior to the acyl stannane sequence.*

LiAlH<sub>4</sub> powder (1.02 g, 27.0 mmol) was suspended in 50 mL of THF. Over a period of 15 minutes, a solution of EtOH (1.24 g, 27.0 mmol) in 5 mL of THF was added with vigorous evolution of hydrogen gas after which (S)-1,1 $\phi$ -bi-2-naphthol (7.73 g, 27.0 mmol) in 50 mL of THF was added by

cannula over 1 hour. The resulting milky solution was refluxed for 1 hour and put aside to cool to room temperature. The solution was then cooled to  $-78^{\circ}$  and a solution of acyl stannane **48** in 45 mL of THF was added by cannula over 1 hour. After stirring for 16 hours at  $-78^{\circ}$  the solution was quenched at  $-78^{\circ}$  with dilute aqueous  $\text{NH}_4\text{Cl}$  (100 mL) over 0.5 hour. The solution was left to come to room temperature and then diluted with water and ether. The layers were separated and the aqueous phase was diluted with 1 M HCl and extracted with ether. The organic extracts were combined, dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The residual hydroxy stannane **48a** (yellow oil) and binaphthol (white powder) were triturated twice with hexane. The binaphthol was recovered by filtration and the hexane extracts were concentrated under reduced pressure to afford crude hydroxy stannane.

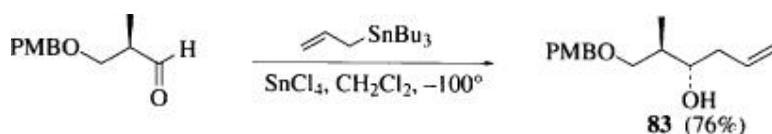
The hydroxy stannane was dissolved in  $\text{CH}_2\text{Cl}_2$  and cooled to  $0^{\circ}$ . Diisopropyl-ethylamine (2.5 mL, 27.0 mmol) was added followed by *t*-butyldimethylsilyl triflate (TBSOTf, 4.96 mL, 21.6 mmol). The reaction mixture was stirred overnight to ensure complete isomerization. The reaction was then quenched with saturated  $\text{NaHCO}_3$  and the aqueous layer was extracted three times with  $\text{CH}_2\text{Cl}_2$ . The combined organic extracts were dried over sodium sulfate and the solvent was removed under reduced pressure. The material was purified by column chromatography on silica gel with hexane as eluent affording 2.6 g (42%) of stannane **50**:  $[\alpha]_{\text{D}}^{25} 117^{\circ}$  (c 1.6,  $\text{CHCl}_3$ ); IR (film) 3563, 3450  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.99 (dd,  $J = 4.8, 1.0$  Hz, 1H), 4.24 (ddd,  $J = 11.1, 5.7, 1.0$  Hz, 1H), 2.55 (dq,  $J = 11.0, 6.4$  Hz, 1H), 1.64–1.39 (m, 6H), 1.40–1.12 (m, 18H), 1.02–0.69 (m, 20H), 0.92 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  134.0, 115.1, 33.4, 32.0, 30.6, 29.7, 29.5, 29.4, 27.7, 25.8, 23.0, 22.8, 18.4, 14.2, 13.8,  $-2.8, -5.0, -5.3$ .



7.1.1.2. (*E,E*)-(7*S*,8*S*)-8-(*tert*-Butyldimethylsilyloxy)-2-methyloctadeca-5,9-die *n*-7-ol (**51**) [Reaction of a Chiral  $\gamma$ -(Silyloxy)allylstannane with an  $\alpha, \beta$ -Unsaturated Aldehyde] (114)

A solution of stannane **50** (552 mg, 0.97 mmol) and 6-methyl-2-heptenal (67 mg, 0.54 mmol) in  $\text{CH}_2\text{Cl}_2$  was cooled to  $-78^{\circ}$ ,  $\text{BF}_3 \cdot \text{OEt}_2$  (96  $\mu\text{L}$ , 0.94 mmol) was added, and the mixture was stirred for 1.5 hours. TLC analysis indicated that the aldehyde had not been consumed so additional  $\text{BF}_3 \cdot \text{OEt}_2$  (100  $\mu\text{L}$ ,

0.98 mmol) was added. After 1 hour, the reaction was quenched with saturated NaHCO<sub>3</sub> solution and the aqueous layer was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried over sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel with 2.5% EtOAc in hexane as eluent to afford 213 mg (73%) of adduct **51**: IR (film) 3563, 3450 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.64 (m, 2H), 5.35 (m, 2H), 3.84 (m, 2H), 2.04 (m, 4H), 1.56 (m, 1H), 1.46–1.08 (m, 16H), 1.03–0.73 (m, 9H), 0.90 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 133.8, 133.7, 129.6, 128.4, 77.9, 76.0, 38.3, 32.2, 31.9, 30.3, 29.5, 29.3, 29.2, 29.1, 27.4, 25.9, 22.7, 22.6, 22.5, 18.2, 14.1, – 3.8, – 4.7; Anal. Calcd for C<sub>25</sub>H<sub>50</sub>O<sub>2</sub>Si : C, 73.10; H, 12.27. Found: C, 73.00; H, 12.24.



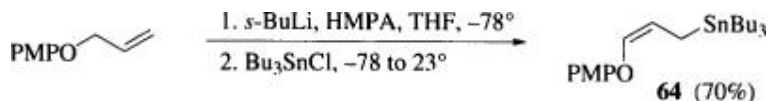
#### 7.1.1.3. (2R,3S)-1-(4-Methoxybenzyloxy)-2-methylhex-5-en-3-ol (**83**)

[Reaction of an Allylstannane with an  $\alpha$ -Chiral  $\beta$ -Alkoxyaldehyde] (**60**)

To a cooled (–100°) solution of tri-*n*-butylallylstannane (1.95 g, 5.89 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (12.0 mL) was added dropwise a solution of tin tetrachloride in CH<sub>2</sub>Cl<sub>2</sub> (5.89 mL, 1.0 M, 5.89 mmol) at –100°. After addition was complete, the solution was stirred for 15 minutes, and a solution of (*R*)-3-(4-methoxybenzyloxy)-2-methylpropanal (754 mg, 3.93 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.6 mL) was added dropwise via cannula. The mixture was stirred at –100° for 1 hour, quenched with saturated aqueous NaHCO<sub>3</sub> solution, and brought gradually to room temperature. The aqueous layer was extracted with Et<sub>2</sub>O, and the combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 20% Et<sub>2</sub>O in hexanes) to give 0.747 g (2.99 mmol, 76%) of **83** and its 3-*R* stereoisomer (20:1) as a colorless oil: R<sub>f</sub> 0.32 (50% Et<sub>2</sub>O in

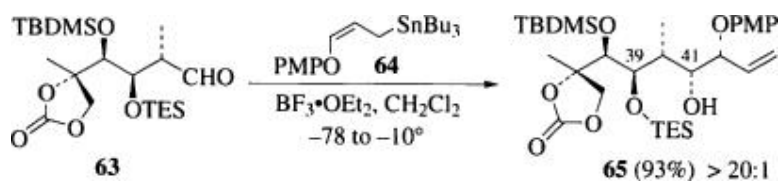
hexanes, PMA);  $[\alpha]_D^{25} -6.46^\circ$  (c 1.30, CHCl<sub>3</sub>); IR (film) 3463 (br), 2959, 1612,

1513, 1248, 1089, 1036, 820 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.25 (AAϕ of AAϕBBϕ, 2H), 6.87 (BBϕ of AAϕBBϕ, 2H), 5.88 (m, 1H), 5.10 (m, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.57 (m, 2H), 3.44 (dd, *J* = 7.1, 9.2 Hz, 1H), 3.30 (s, 1H), 2.32 (m, 1H), 2.18 (m, 1H), 1.86 (m, 1H), 0.90 (d, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 159.2, 135.2, 129.9, 129.2, 117.1, 113.8, 75.0, 74.4, 73.0, 55.2, 39.3, 37.79, 13.78; HRMS (CI, *m/z*): [*M*<sup>+</sup>] calcd for C<sub>15</sub>H<sub>22</sub>O<sub>3</sub>, 250.1569; found 250.1565.



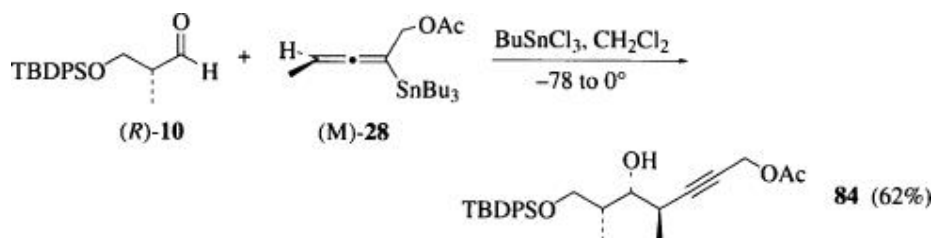
7.1.1.4. (Z)- $\gamma$ -(4-Methoxyphenoxy)allyltributylstannane (**64**) [Preparation of an Achiral  $\gamma$ -(Alkoxy)allylstannane] (159)

To a solution of 4-methoxyphenyl allyl ether (14.8 g, 90 mmol) in 150 mL of THF at  $-78^\circ$ , was added 75 mL of *s*-BuLi (1.27 M in cyclohexane, 95 mmol), followed immediately by the addition of HMPA (15 mL). The solution was stirred at  $-78^\circ$  for 15 minutes, then  $\text{Bu}_3\text{SnCl}$  (26 mL, 96 mmol) was added via syringe, and the  $-78^\circ$  bath was removed. The solution was stirred for 2 hours at ambient temperature, then quenched with  $\text{NH}_4\text{Cl}$  (saturated), diluted with hexanes and EtOAc, washed with  $\text{NaHCO}_3$  (saturated), and then washed with  $\text{H}_2\text{O}$ . The organic phase was dried over  $\text{MgSO}_4$  and concentrated to afford a crude oil, which was purified by distillation at reduced pressure (ca 0.3 mm Hg; bp 195 to  $205^\circ$ ), providing 28.7 g (70%) of title compound **64**. The distilled product was used as is for the next reaction, however, a small portion was purified by HPLC (21-mm column, 8 ml/min, 100% hexanes, 15 minutes; then 20% EtOAc/hexanes, 10 minutes) to afford a sample for analytical characterization: IR (thin film) 3043, 2956, 2925, 2871, 2853, 1652, 1591, 1505, 1465, 1442, 1418, 1373, 1340, 1292, 1241, 1225, 1180, 1153, 1102,  $1052\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.94–6.90 (m, 2H), 6.86–6.83 (m, 2H), 6.19–6.14 (m, 1H), 4.99–4.94 (m, 1H), 3.78 (s, 3H), 1.87–1.72 (m, 2H), 1.58–1.45 (m, 6H), 1.35–1.26 (m, 6H), 0.91–0.87 (m, 15H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  154.7, 152.0, 137.4, 116.9, 114.5, 111.4, 55.7, 29.1, 27.4, 13.7, 9.4, 6.0; HRMS (CI,  $\text{NH}_3$ )  $m/z$ :  $[\text{M} - \text{C}_4\text{H}_9]^+$  calcd for  $\text{C}_{18}\text{H}_{29}\text{O}_2\text{SiSn}$ , 397.1190; found, 397.1184. The configuration of stannane **64** was confirmed by the observation of  $^1\text{H}$  nOe's between the two olefinic protons.



7.1.1.5. 4-[(1*S*,2*R*,3*R*,4*R*,5*R*)-1-(*tert*-Butyldimethylsilyloxy)-4-hydroxy-5-(4-methoxyphenoxy)-3-methyl-2-triethylsilanyloxyhept-6-enyl]-4-methyl-1,3-dioxolan-2-one (**65**) [Reaction of an Achiral  $\gamma$ -(Alkoxy)allylstannane with a Chiral Aldehyde] (159)

To a  $-78^{\circ}$  solution of crude 2,3-anti aldehyde **63** (8.62 mmol) and  $\gamma$ -(alkoxy)allylstannane **64** (5.5 g, 12.1 mmol) in 25 mL of  $\text{CH}_2\text{Cl}_2$  was added  $\text{BF}_3 \cdot \text{OEt}_2$  (2.2 mL, 17.4 mmol). The reaction mixture was stirred at  $-78^{\circ}$  for 16 hours, then warmed slowly to  $-20^{\circ}$  and quenched by the addition of 10 mL  $\text{NaHCO}_3$  (saturated). The cold bath was removed and the solution was brought to room temperature. The solution was diluted with EtOAc and washed with  $\text{NaHCO}_3$  (saturated) followed by brine. The organic layer was dried over  $\text{MgSO}_4$ , filtered and concentrated to provide title compound **65** as a crude oil (>20:1 ds by  $^1\text{H}$  NMR analysis) which was purified by flash column chromatography [160 g  $\text{SiO}_2$ , 18:1 hexanes/EtOAc (1 L); 9:1 hexanes/EtOAc (1 L); 5:1 hexanes/EtOAc (1 L)] providing 4.92 g of analytically pure **65** (93% over 2 steps):  $[\alpha]_D^{25} +16.3^{\circ}$  (c 1.0,  $\text{CH}_2\text{Cl}_2$ ); IR (thin film) 3586, 2955, 2881, 1808, 1644, 1614, 1593, 1505, 1471, 1417, 1392, 1365, 1225, 1101, 1006  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.89–6.86 (m, 2H), 6.82–6.79 (m, 2H), 5.68 (ddd,  $J = 17.6, 10.4, 7.4$  Hz, 1H), 5.33–5.28 (m, 1H), 4.70 (d,  $J = 7.8$  Hz, 1H), 4.37 (dd,  $J = 8.2, 8.2$  Hz, 1H), 4.05 (d,  $J = 2.7$  Hz, 1H), 3.99 (d,  $J = 8.5$  Hz, 1H), 3.95 (d,  $J = 7.8$  Hz, 1H), 3.84 (dd,  $J = 9.5, 2.7$  Hz, 1H), 3.76 (s, 3H), 2.57 (s, 1H), 1.6–1.5 (m, 1H), 1.52 (s, 3H), 1.06 (d,  $J = 6.6$  Hz, 3H), 1.01 (t,  $J = 7.9$  Hz, 9H), 0.90 (s, 9H), 0.75–0.66 (m, 6H), 0.15 (s, 3H), 0.14 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  154.3, 154.2, 151.8, 134.4, 120.2, 118.4, 114.5, 86.9, 84.0, 77.2, 75.1, 71.7, 70.4, 55.6, 36.1, 25.8, 23.8, 18.1, 10.2, 7.1, 5.3,  $-4.1$ ,  $-4.8$ ; HRMS (CI,  $\text{NH}_3$ )  $m/z$ :  $[\text{M} + \text{NH}_4]^+$  calcd for  $\text{C}_{31}\text{H}_{58}\text{Si}_2\text{NO}_8$ , 628.3701; observed, 628.3699.



7.1.1.6. (2R,3R,4R)-(+)-1-(tert-Butyldiphenylsilyloxy)-2,4-dimethyl-7-acetoxy-5-heptyn-3-ol (**84**) [Standard Procedure with Butyltin Trichloride]

To a solution of allenic stannane (M)-**28** (0.133 g, 0.320 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.7 mL) at  $-78^{\circ}$  was added  $\text{BuSnCl}_3$  (0.056 mL, 0.335 mmol). The dry ice bath was removed, and after 5 hours, aldehyde (R)-**10** (95.0 mg, 0.291 mmol) was added in  $\text{CH}_2\text{Cl}_2$  (0.2 mL). After 18 hours, the reaction was quenched with 10% HCl solution (0.5 mL) and the solution was extracted with  $\text{Et}_2\text{O}$ . The combined organic layers were washed with brine and dried over anhydrous  $\text{MgSO}_4$ . Triethylamine (0.5 mL) was added, and the mixture was vigorously stirred at  $0^{\circ}$  for 15 minutes. The resulting white slurry was filtered through a



pad of Celite with Et<sub>2</sub>O, and the filtrate was concentrated to give the crude alcohol as a yellow oil. The residue was chromatographed on silica gel (first with 25% Et<sub>2</sub>O in hexanes, and then with 25% EtOAc in hexanes) yielding 68.9 mg (62%) of alcohol **84** as a clear oil. [α]<sub>D</sub> + 3.6° (c 6.27, CHCl<sub>3</sub>).

## 8. Tabular Survey

An effort has been made to tabulate all examples of additions to aldehydes, ketones, and imines using allylstannane reagents reported from the mid-1980s to the end of 2000. In general, the reactions are arranged in order of increasing carbon count of the allylstannane reagent, excluding functional groups such as esters, ethers, amines, etc. The reactions using simple allylstannanes that are promoted by a Lewis acid are listed in [Table 1](#). The reactions promoted by heat are listed in [Table 2](#). The catalytic enantioselective reactions are listed in [Table 3](#). The reactions promoted by a chiral borane are listed in [Table 4](#). The reactions using  $\alpha$ -(alkoxy)allylstannanes that are promoted by a Lewis acid are listed in [Table 5](#). The reactions using achiral  $\gamma$ -(alkoxy)allylstannanes that are promoted by a Lewis acid are listed in [Table 6](#). The reactions using chiral  $\gamma$ -(alkoxy)allylstannanes that are promoted by a Lewis acid are listed in [Table 7](#). The reactions using allenylstannanes are listed in [Table 8](#). The reactions using propargylstannanes are listed in [Table 9](#). Intramolecular additions of allylstannane-aldehydes are listed in [Table 10](#). [Table 11](#) contains reactions using the allylstannanes that are not easily classified under the above definitions.

Isolated yields of the combined allylation products are included in parentheses and a dash, (–), indicates that no yield was reported. Where an enantiomeric excess is reported, it relates to the major product of a reaction.

The following abbreviations have been used in the tables:

BINOL	binaphthol
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
BOM	benzyloxymethyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
FSPE	Fluorous Solid Phase Extraction
LDA	lithium diisopropylamide
MEM	methoxyethoxymethyl
MOM	methoxymethyl
PMB	<i>p</i> -methoxybenzyl
PMP	<i>p</i> -methoxyphenyl
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl

TBS	<i>tert</i> -butyldimethylsilyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THP	2-tetrahydropyranyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Ts	<i>p</i> -toluenesulfonyl

**Table 1. Thermally Promoted Addition of Allylic Tributylstannanes to Aldehydes**

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**Table 2A. Lewis Acid Promoted Addition of Allylic Tributylstannanes to Achiral Aldehydes**

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**Table 2B. Lewis Acid Promoted Addition of Allylic Tributylstannanes to Chiral Aldehydes**

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**Table 3. Addition of Allylic Tributylstannanes via Transmetalation**

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**Table 4. Lewis Acid Promoted Addition of  $\alpha$  -(Alkoxy)allylstannanes to Aldehydes**

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**Table 5. Addition of  $\alpha$  -(Alkoxy)allylstannanes to Aldehydes via Transmetalation**

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**Table 6A. Lewis Acid Promoted Addition of  $\gamma$  -(Alkoxy)allylstannanes to Achiral Aldehydes**

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**Table 6B. Lewis Acid Promoted Addition of  $\gamma$  -(Alkoxy)allylstannanes to Chiral Aldehydes**

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**Table 7. Intramolecular Additions of Allylstannanyl Aldehydes**

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**Table 8. Lewis Acid Promoted Addition of Allenylstannanes to Aldehydes**

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**Table 9. Addition of Allenylstannanes to Aldehydes via Transmetalation**

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**Table 10. Addition of 4-Alkoxy-2-pentenylstannanes to Aldehydes via Transmetalation**

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**Table 11. Addition of Allylstannanes to Imines**

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**Table 12A. Lewis Acid Promoted Addition of Other Allylstannanes to Aldehydes and Ketones**

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**Table 12B. Addition of Other Allylstannanes to Aldehydes via Transmetalation**

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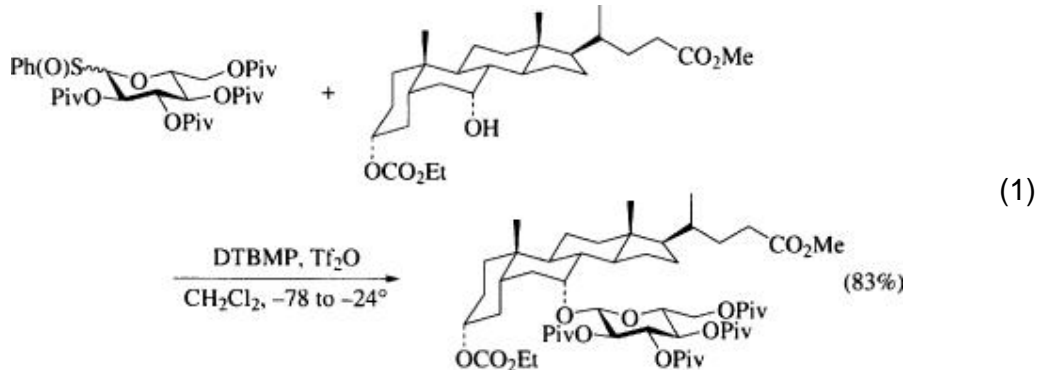
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# Glycosylation with Sulfoxides and Sulfinates as Donors or Promoters

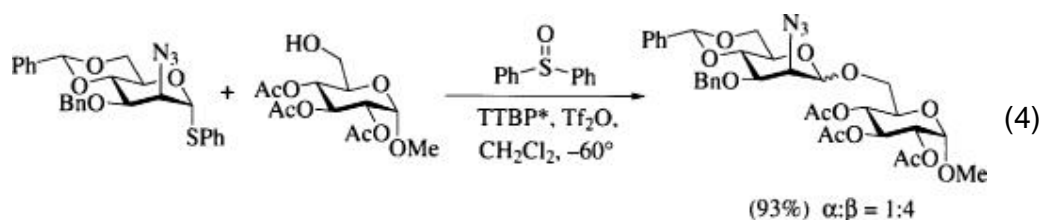
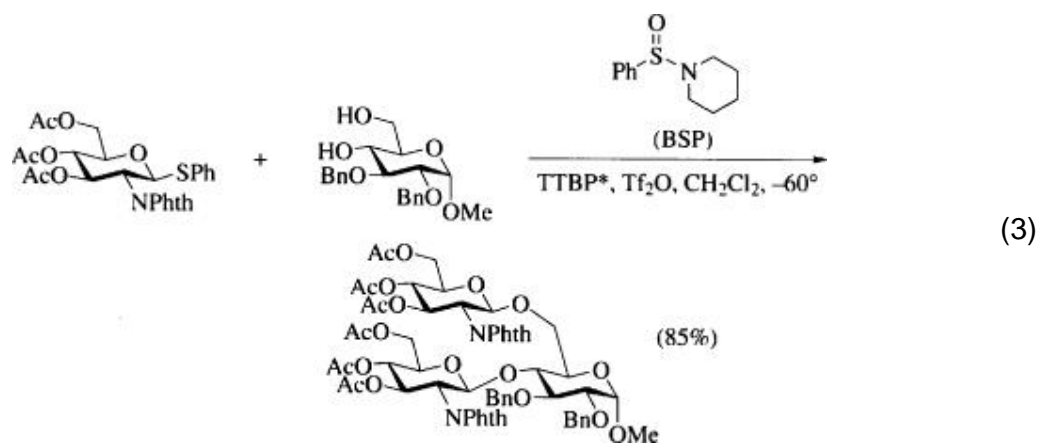
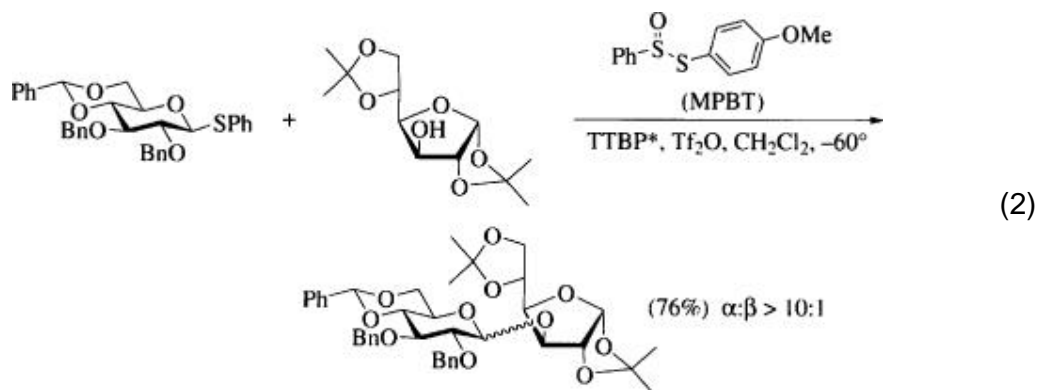
David Crich, University of Illinois at Chicago, Chicago, Illinois, USA  
Linda B. L. Lim, University of Brunei Darussalam, Negara Brunei Darussalam

## 1. Introduction

The efficient, stereocontrolled formation of glycosidic bonds is arguably the most fundamental reaction in glycoscience, the study of the chemistry and biology of carbohydrates, their oligomers, and conjugates. (1-8) This chapter surveys four recent distinct glycosylation methods united by the common theme of employing sulfoxides, or closely related sulfinates, either in the glycosyl donor itself or as an integral part of the promoter. In the first method, hereinafter referred to as the sulfoxide method, (9) a glycosyl sulfoxide, the donor, is coupled to an acceptor alcohol by means of an activating agent to give the glycosidic bond (Eq. 1). The activating agent is typically triflic anhydride, (9) but trimethylsilyl triflate, (10) triflic acid, (11, 12) various Lewis (13) and mineral acids, (14, 15) and even iodine (16) have also been used.

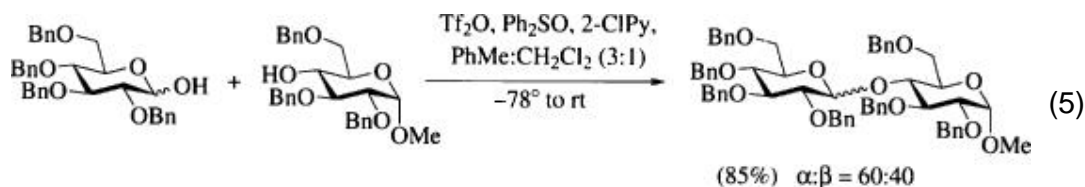


In the second method the donor is a thioglycoside. It is activated by means of a promoter derived in situ from reaction of trifluoromethanesulfonic anhydride and a thiosulfinate (Eq. 2), a sulfinamide (Eq. 3), or diphenyl sulfoxide (Eq. 4) before coupling to an acceptor alcohol. (17-19) These closely related methods will be individually termed the thioglycoside/sulfinate, thioglycoside/sulfinamide, and the thioglycoside/sulfoxide methods. Collectively, they will simply be called the thioglycoside method.

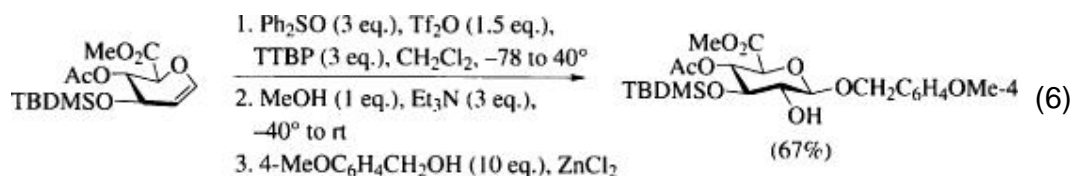


The third method is a dehydrative coupling. In it the free anomeric hydroxy group of an aldose is activated for coupling to an alcohol with diphenyl sulfoxide and trifluoromethanesulfonic anhydride (Eq. 5). (20, 21) Other reaction sequences are known in which a glycosidic bond is formed from a hemiacetal and an alcohol by formal extrusion of a molecule of water, (22) but this chapter is only concerned with the recent variation in which dehydration is achieved by means of the combination of diaryl sulfoxides and trifluoromethanesulfonic anhydride.





The direct oxidative glycosylation of glycals, the last of the methods and here-inafter termed the oxidative method, differs significantly from the first three methods insofar as it does not employ a traditional anomeric derivative as glycosyl donor but derives one by the formal oxidation of a glycal (Eq. 6). (23) The method is related to the former ones by the use of the combination of a sulfoxide, typically diphenyl sulfoxide, and triflic anhydride to generate a potent electrophile as the essential first step of the reaction.



At some time in the activation process all four methods typically involve the reaction of a sulfoxide or sulfinic acid with trifluoromethanesulfonic anhydride. All four methods liberate trifluoromethanesulfonic acid and this is typically, but not always, buffered by the addition of a hindered, non-nucleophilic base such as 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), (9) 2,6-di-*tert*-butylpyridine (DTBP), (24) 2,4,6-tri-*tert*-butylpyridine (TTBP) (25) or, more recently and more economically, 2,4,6-tri-*tert*-butylpyrimidine (TTBP\*), (26) All four methods possess the distinct advantage of using readily prepared, stable glycosyl donors. Three of them are metal-free and two so far have been shown to enable coupling to even the most hindered unreactive alcohols in a matter of minutes at low temperature. They therefore represent some of the most powerful methods available for the formation of glycosidic linkages.

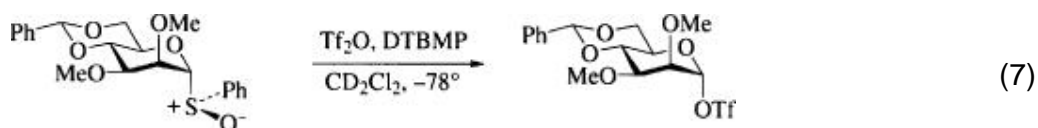
The formation of C-glycosides from glycosyl sulfoxides by metalation (27, 28) and alkylation, (29) a process that involves the formation of glycosyl carbanions as intermediates, is not a subject of this chapter.

## 2. Mechanism and Stereochemistry

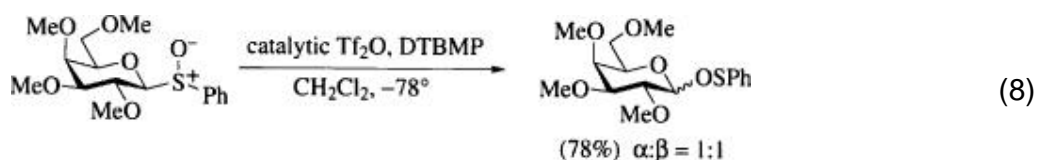
### 2.1. Nature of the Reactive Intermediates

The formation of a glycosidic bond from an activated donor and an acceptor alcohol is a complex event that can follow any one of a range of pathways spanning stereospecific  $S_N2$  displacements, through stereoselective displacements on contact ion pairs in equilibrium with covalently bound donors, to  $S_N1$  reactions on solvent-separated and free ion pairs. (30, 31) The situation is further complicated by the possibility of in situ anomerization of the donor (30, 31) and of neighboring group participation, or anchimeric assistance, by ester groups usually on O-2 but also in more remote positions. (31-33) To further complicate the situation, the actual mechanism operating can shift between any one of a continuum of possibilities depending on solvent, temperature, and additives. In view of this complexity, and the extra twist added by the heterogeneous nature of many classical, metal-promoted glycosylations, it is not surprising that detailed studies of mechanism and reactivity are few and far between. (34-41) For example, even for such entrenched concepts as neighboring group participation there are few mechanistic studies. (42-46) The various methods that constitute this chapter are no different from other glycosylation reactions in this respect; the precise details of the mechanism for formation of the glycosidic bond are not known. Considerable effort, however, has been expended on determining the identity of the glycosylating species formed upon activation of the donor.

In the sulfoxide glycosylation the nature of the intermediate formed on activation is a function of how the reaction is conducted. When the sulfoxide is activated with triflic anhydride prior to addition of the acceptor (pre-activation), glycosyl triflates are formed very rapidly and serve as the actual glycosyl donors (Eq. 7). (47, 48) When the sulfoxide is activated in the presence of the acceptor it is likely that the glycosyl cation is captured directly by the acceptor alcohol. (47) In those reactions proceeding via the glycosyl triflate, it is not yet clear whether the leaving group is displaced directly by the acceptor alcohol in an  $S_N2$  reaction or whether the covalently bound triflate serves as a reservoir for the release of transient contact oxocarbenium ion/triflate ion pairs that are trapped stereoselectively. (49, 50) Evidence for the triflate mechanism derives from low temperature NMR studies in which an intermediate was identified whose characteristics were most consistent with an  $\alpha$ -mannosyl triflate. (47, 48) This same intermediate was also detected upon exposure of the corresponding mannosyl bromide to silver triflate (47) and upon treatment of a mannosyl fluoride with trimethylsilyl triflate. (21) Together, these observations lend considerable support for the proposed glycosyl triflate.



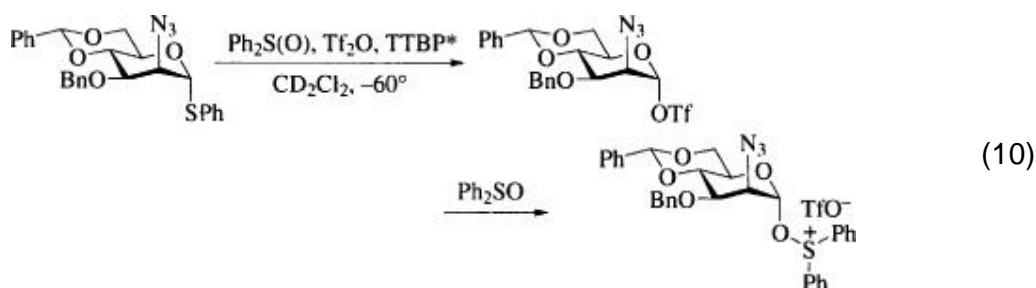
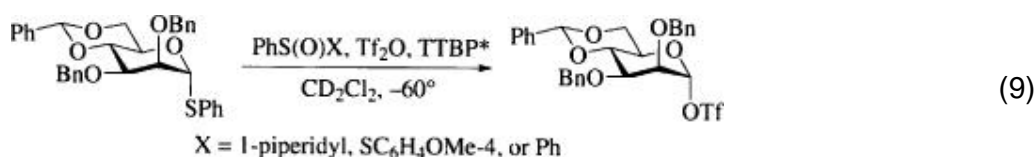
Isomerization of some glycosyl sulfoxides to the corresponding sulfenate esters can occur upon exposure to catalytic triflic anhydride (Eq. 8). (51) These glycosyl esters could be isolated and were fully characterized. They were shown to be glycosyl donors in their own right, but their rate of reaction is slow. A mechanism was proposed for their formation and, on this basis, conditions were prescribed to minimize their formation. These conditions, known as inverse addition, involve slow addition of the sulfoxide to a mixture of triflic anhydride and the base in an appropriate solvent. (51)



Nothing is known at the present time about the nature of the species formed upon activation of glycosyl sulfoxides with Brønsted and Lewis acids, (13-15) although it is reasonable to assume in the case of trimethylsilyl triflate (10) and triflic acid (11, 12) that glycosyl triflates (10) are the reactive species. It has been speculated that glycosyl iodides may be formed as intermediates when iodine is the activating species for glycosyl sulfoxides. (16)

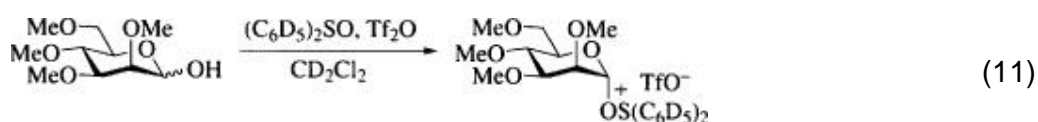
In the thioglycoside method a mixture of the sulfinate, sulfinamide or sulfoxide promoter, the thioglycoside, and the base (TTBP\* or DTBMP) are stirred at  $-60^\circ$  followed by addition of triflic anhydride. This leads to the formation of an activated promoter: a powerful thiophile that rapidly converts the thioglycoside into a glycosyl triflate as obtained in the sulfoxide method (Eq. 9). Thereafter the mechanism appears to be the same as that of the sulfoxide method with the triflate being displaced either directly or via the intermediacy of a contact ion pair on addition of the acceptor alcohol. (17-19) Given their mechanistic commonalities, the stereochemical outcomes of thioglycoside couplings closely parallel those of the sulfoxide method. A possible caveat applies in the case of the mechanism of the thioglycoside/sulfoxide method. When activation of the thioglycoside is conducted with one equivalent of diphenyl sulfoxide, it is to be expected that the reactive intermediate formed is the glycosyl triflate, just as in the thioglycoside/sulfinate and sulfinamide variants of the method. However, if excess diphenyl sulfoxide is employed then, in the light of the

mechanistic experiments on the dehydrative method, (21) it is to be expected that the triflate will be displaced by the excess reagent leading to the formation of a glycosyl sulfonium salt (Eq. 10). Published experimental data (19) for the thioglycoside/sulfoxide method describe the use of 2.8 equivalents of diphenyl sulfoxide and only 1.4 of triflic anhydride; under such conditions the thioglycoside/sulfoxide method can be seen to form a bridge to the dehydrative method.

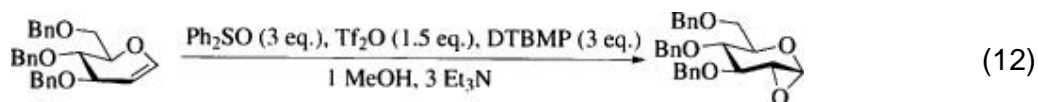


In the dehydrative method, triflic anhydride is added to a solution of the hemiacetal donor and diphenyl sulfoxide at  $-78^\circ$  resulting in the formation of an *O*-glycosyl sulfonium salt by attack of the hemiacetal on the initially formed (trifluoromethanesulfonyloxy)diphenylsulfonium triflate (Eq. 11). Addition of the acceptor together with the base, 2-chloropyridine, then results in displacement of the sulfoxide and formation of the glycosidic bond. (21)  $^{18}\text{O}$ -Labeling experiments were used to provide support for attack of the hemiacetal on the sulfoxide sulfur of the activated reagent and to rule out the alternative possibility that (trifluoromethanesulfonyloxy)diphenylsulfonium triflate acts as a powerful triflating agent. (21) A further experiment in which diphenyl sulfoxide was added to a preformed glycosyl triflate resulted in the identification, by NMR spectroscopy, of the glycosyl sulfonium salt, presumably the active glycosylating agent. (21) The dehydrative method therefore differs significantly in mechanism from the sulfoxide and thioglycoside/sulfinate methods in so far as glycosyl triflates are not the active glycosylating species. The original protocol calls for the addition of 2-chloropyridine as base concomitantly with the acceptor to the activated hemiacetal. When this same base was added in the absence of the acceptor, NMR spectroscopic experiments indicated that glycosyl pyridinium salts are formed as the major species in solution, and thus

the possibility cannot be excluded that the glycosyl pyridinium salts are the main glycosylating species. Subsequent studies, however, showed that the dehydrative method could be conducted satisfactorily with the much more hindered TTBP\* (52) or TTBP. (53) With these bases the formation of glycosyl pyridinium salts is extremely unlikely, suggesting that such species are not necessary intermediates in this chemistry. Dibenzothiophene oxide is an effective replacement for diphenyl sulfoxide in these coupling reactions as demonstrated by the formation of glycosyl dialkyl phosphates from the hemiacetals and dialkylphosphoric acids. (53) The stereoselectivity of the dehydrative method reflects a typical glycosylation reaction with armed donors providing mainly axial glycosides and disarmed donors affording 1,2-trans glycosides through neighboring group participation.

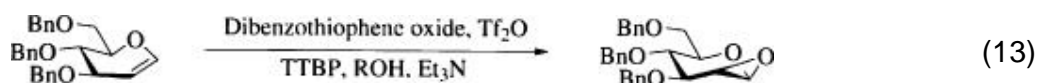


In the glycal method, just as in the dehydrative method, diphenyl sulfoxide reacts rapidly with triflic anhydride to give (trifluoromethanesulfonyloxy)diphenylsulfonium triflate. This potent electrophile then reacts with the glycal to afford an intermediate that is trapped by a second equivalent of diphenyl sulfoxide, now acting as nucleophile. Following the addition of one equivalent of methanol, collapse of the second intermediate, incorporating both equivalents of the sulfoxide, provides the 1,2-anhydrofuranose, which is the glycosylating species (Eq. 12). Experiments with <sup>18</sup>O-labeled diphenyl sulfoxide show that the oxygen substituent incorporated at the 2-position of the final glycoside is sulfoxide derived and confirm the formation of the 1,2-anhydrofuranose. (23, 54, 55)

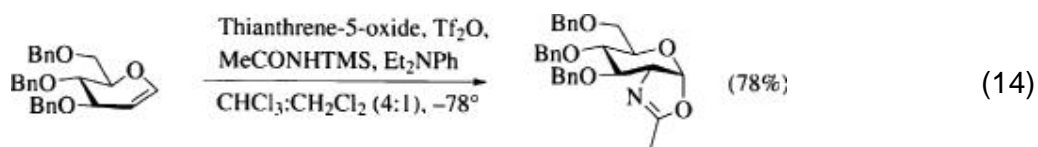


When the glycal is treated with diphenyl sulfoxide, a 1,2-anhydrofuranose with the gluco-orientation is formed. The orientation of the actual glucoside,  $\alpha$ - or  $\beta$ -, obtained upon opening of the anhydro sugar is a function of the conditions employed, as is well documented for 1,2-anhydroglucose derivatives formed by other methods. (55, 56) In most reactions conducted with 1,2-anhydroglucose generated by means of diphenyl sulfoxide and triflic anhydride, zinc chloride has been used to assist nucleophilic opening of the

oxirane to give the  $\beta$ -glucoside. (23) However, with the less reactive glucose 4-OH group as nucleophile it was noted that scandium triflate was required as Lewis acid which resulted in the formation of the  $\alpha$ -glucoside, thereby demonstrating the sensitivity of the opening to both the nucleophile and the reagent. (23) When diphenyl sulfoxide is replaced by dibenzothiophene oxide the reaction takes a different stereochemical course to ultimately yield  $\alpha$ -mannosides. (54) It is thought that the first equivalent of activated sulfoxide attacks the  $\alpha$  face of the glucal and that the steric and conformational properties of this first-formed intermediate are now such that ensuing nucleophilic attack by the second equivalent of sulfoxide now takes place on the  $\beta$  face, leading eventually to the 1,2-anhydrofuranose with the manno-orientation (Eq. 13). Again NMR and  $^{18}\text{O}$ -labeling experiments support the gross features of this mechanism. (55)



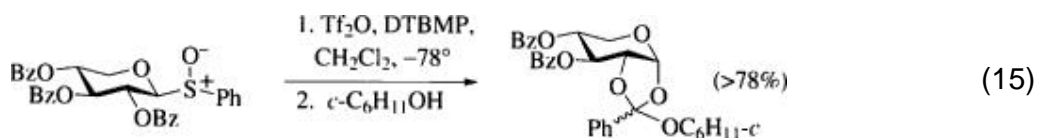
A third variant of the glycal method employs thianthrene-5-oxide as sulfoxide and a primary amide as first nucleophile; addition of base results in formation of oxazolines (Eq. 14). These heterocycles are known precursors to 2-acetamido-2-deoxy- $\beta$ -glycosides following ring opening under acidic conditions. (57, 58) The initial work employed *N*-trimethylsilylacetamide as the nitrogen nucleophile leading to the formation of 2-acetamido-2-deoxy- $\beta$ -glycosides directly. (57) In subsequent work, however, it was demonstrated that a range of primary amides functioned well, without the need for silylation, resulting overall in the formation of a range of functionalized *N*-acyl derivatives of 2-amino-2-deoxy glycosides. (58)



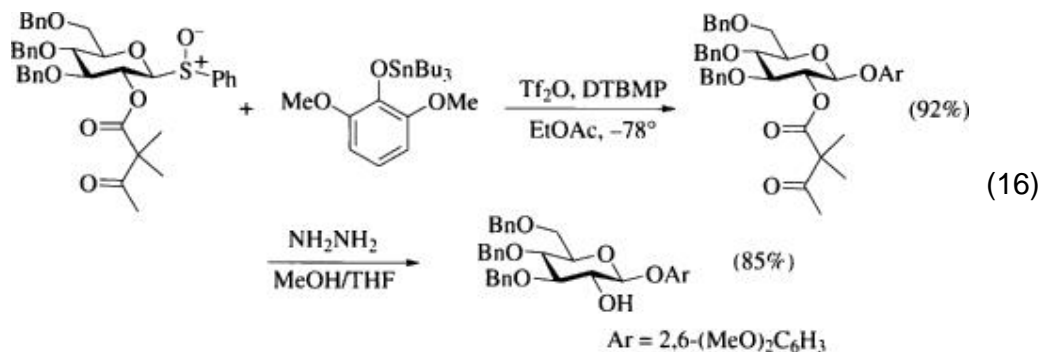
## 2.2. Neighboring Group Participation

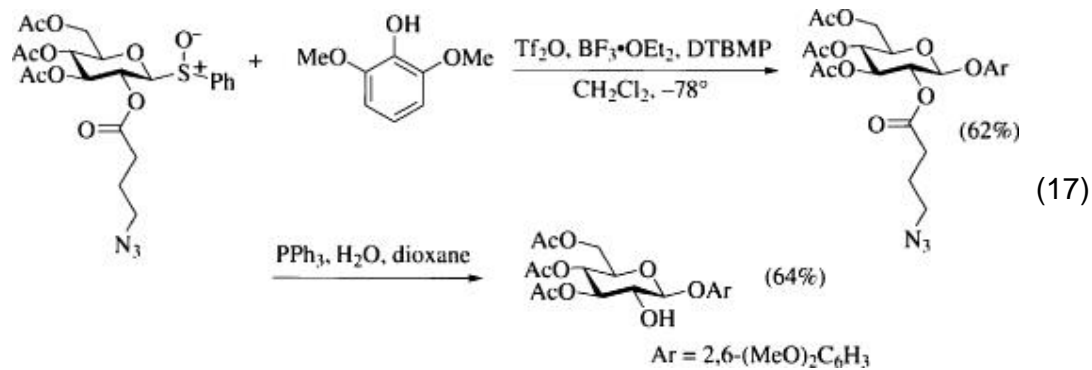
As in all glycosylation reactions, the stereochemical outcome of a sulfoxide coupling is a function of solvent and of the protecting groups in both the donor and the acceptor. Most importantly, when O-2 of the glycosyl donor is protected as an ester, neighboring group participation exerts a strong stereodirecting influence (Eq. 1). Among the systems described here, neighboring group participation can contribute to the stereochemical outcome

of the sulfoxide method, the thioglycoside method, and the dehydrative method. Unless a more remote position is involved, it is obviously not an issue in the glycal method. As all three susceptible methods are usually conducted in the presence of a base to buffer the triflic acid formed, orthoester formation can be a problem (Eq. 15). (18, 42, 59-63)

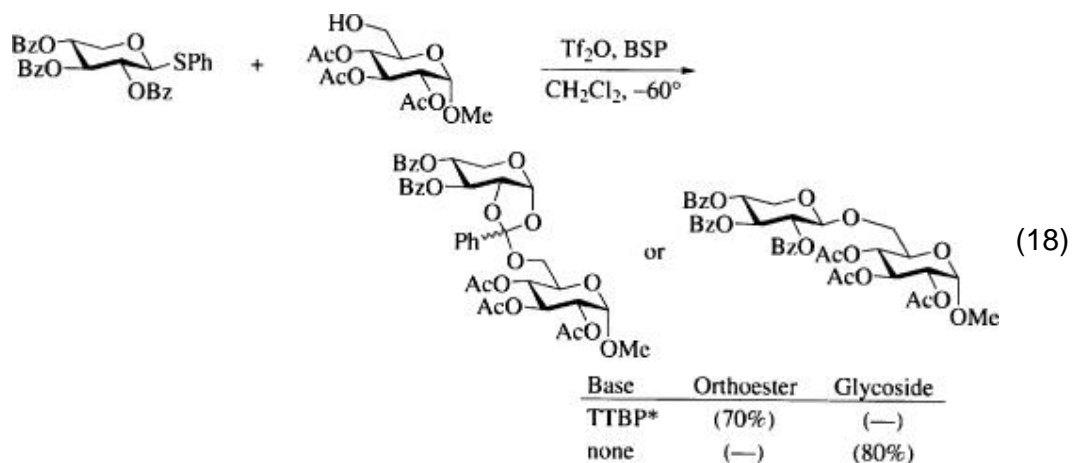


The paradoxical requirement of a base to buffer the liberated triflic acid and of an acid or Lewis acid to catalyze the in situ rearrangement of any orthoesters formed to glycosides has been circumvented with the combination of DTBMP and  $\text{BF}_3 \cdot \text{OEt}_2$ . (64) This reagent combination succeeds because DTBMP is too hindered to complex the Lewis acid yet is able to function as a Brønsted base and scavenge triflic acid. The 2,2-dimethylacetoacetyl and 4-azidobutyryl esters, which may be liberated by treatment with hydrazine or triphenylphosphine, respectively, have also been introduced (Eqs. 16 and 17). (64, 65) They enable advantage to be taken of stereo-directing neighboring group participation, with minimization of orthoester formation yet, unlike the more robust pivalates, can be removed under very mild conditions.





Even more simply, the isolation of orthoesters can be avoided in many cases by conducting the reaction in the absence of base (Eq. 18). (18, 64, 66)  
Obviously this is not a suitable remedy when acid-sensitive substrates are employed.

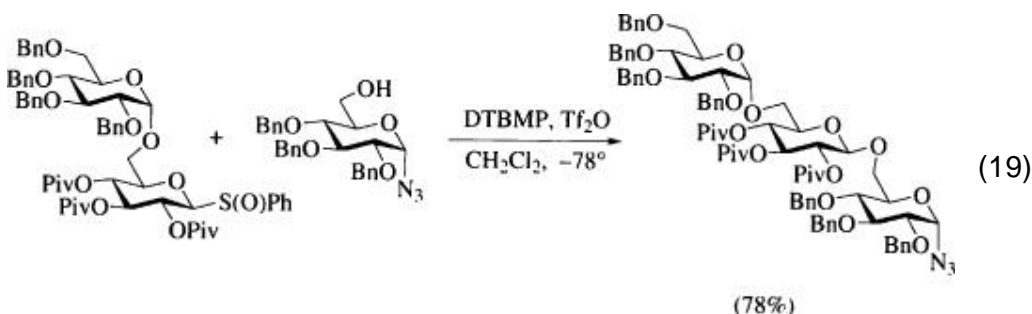




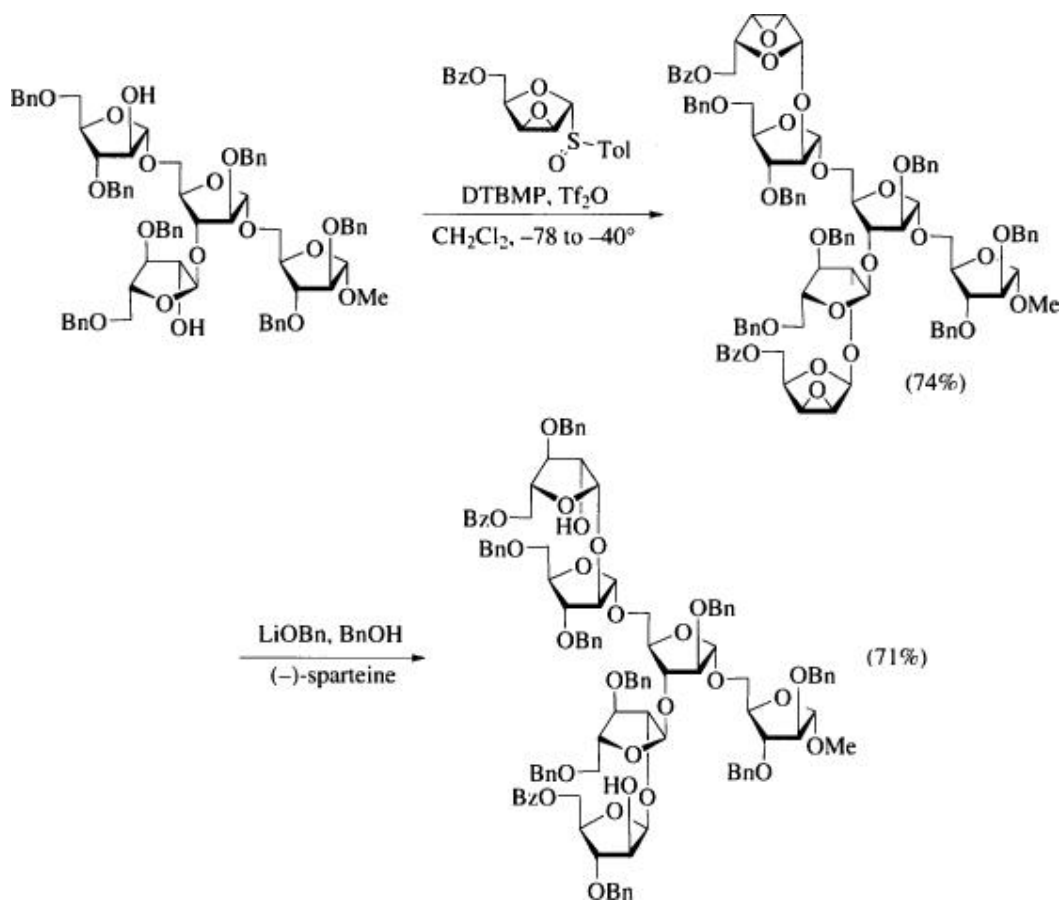
### 3. Scope and Limitations

#### 3.1. Donors

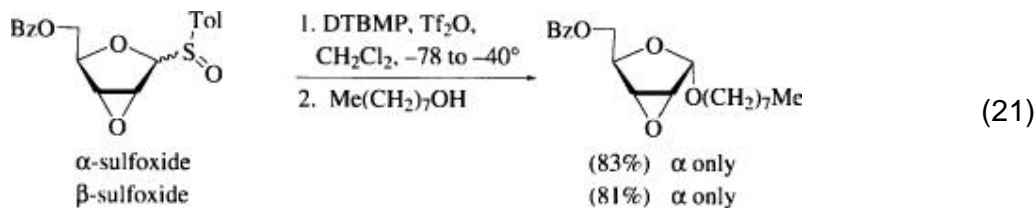
The sulfoxide, thioglycoside, and dehydrative glycosylation methods are applicable together to the direct formation of almost all classes of O-glycosidic bonds, including, at least for the dehydrative method, the sialic acid glycosides. (67) The three methods can be employed with both ether protected donors, so-called (68) armed donors, and with ester protected, or disarmed, donors. The majority of couplings to date have made use of monosaccharide pyranosyl donors but successful couplings with disaccharide donors (Eq. 19), (69, 70) and with furanosyl donors (Eqs. 20 and 21) (71-73) are known, the former even in polymer-supported couplings. (74)



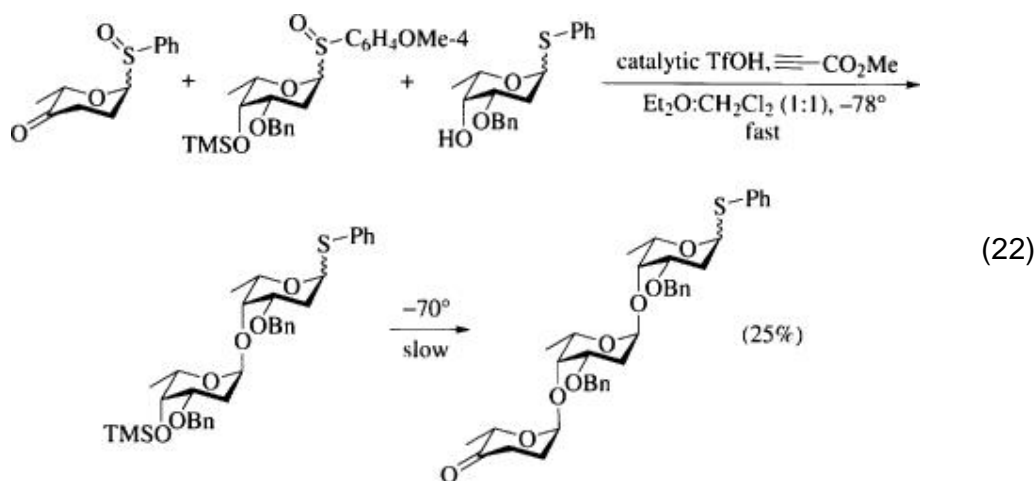
With 2,3-anhydro-lyxofuranosyl sulfoxide donors, glycosylations are highly  $\beta$ -selective, especially when the sulfoxide/trifluoromethanesulfonic anhydride combination is warmed to  $-40^\circ$  before addition of the acceptor. (48, 72, 73) Highly regioselective opening of the epoxide to the arabino product post-glycosylation can be achieved with lithium benzyloxide in the presence of sparteine. This combination of highly diastereoselective coupling and regioselective ring opening is employed to good effect in the final stages of a synthesis of a key hexasaccharide motif from the two mycobacterial cell wall polysaccharides arabinogalactan and lipoarabinomannan (Eq. 20). (72)



When a 2,3-anhydro-ribofuranosyl sulfoxide is employed as donor the  $\alpha$ -product predominates (Eq. 21). In the example depicted in Eq. 21, both anomers of the donor give the same  $\alpha$ -selectivity indicating that the glycosylations do not arise from direct displacements on activated sulfoxides. (72) NMR experiments support the concept of formation of intermediate glycosyl triflates in these 2,3-anhydrofuranoside donors, just as is observed in the pyranoside series, with the triflate oriented trans to the epoxide. (48) With these  $\alpha$ -glycosides, cleavage of the epoxide with alkoxides takes place predominantly with nucleophilic attack at C2. (72) Use of the lyxo- and ribo-2,3-anhydrofuranosyl sulfoxide donors, followed by alkoxide mediated ring opening therefore provides access to the  $\beta$ - and  $\alpha$ -anomers, respectively, of the arabinofuranosides.

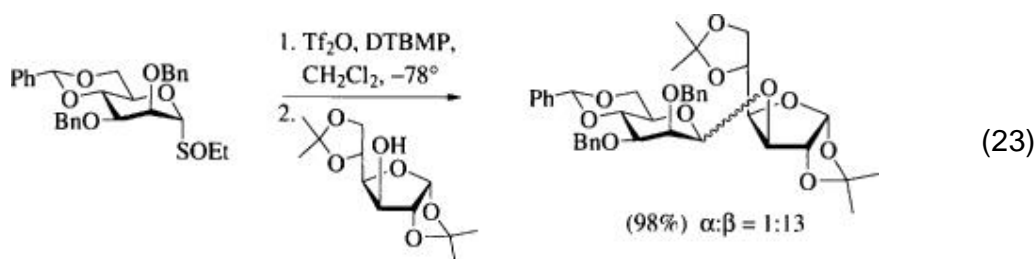


Both alkyl and aryl glycosyl sulfoxides are activated rapidly by triflic anhydride, and they can be used almost interchangeably. On occasion this presents advantages when the solubility of a particular sulfoxide in the required solvent is a problem. Another property of the glycosyl sulfoxides is the good correlation of the rate of acid-catalyzed hydrolysis of S-(para-substituted-phenyl)  $\beta$ -thioglucoside sulfoxides with the Hammett  $\delta_p$  coefficient. (75) In a synthetic context this enables the nucleophilicity of aryl glycosyl sulfoxides to be accentuated or attenuated by the inclusion of electron-donating or -withdrawing groups, respectively, on the aryl ring. This control over reactivity permits the activation of an electron-rich sulfoxide in the presence of an electron-poor cousin. Such differential reactivity has been exploited in a one-pot synthesis of a ciclamycin trisaccharide (Eq. 22). (11, 70) The differential nucleophilicity of an alcohol and a trimethylsilyl ether also contributes to the success of this one-pot synthesis. In the first generation synthesis of the ciclamycin trisaccharide (Eq. 22), (11) methyl propiolate was employed as a scavenger for arenesulfonyl triflates produced in the course of the sulfoxide activation, whereas the later complete synthesis of ciclamycin O itself made use of 4-allyl-1,2-dimethoxybenzene for this purpose. (70)

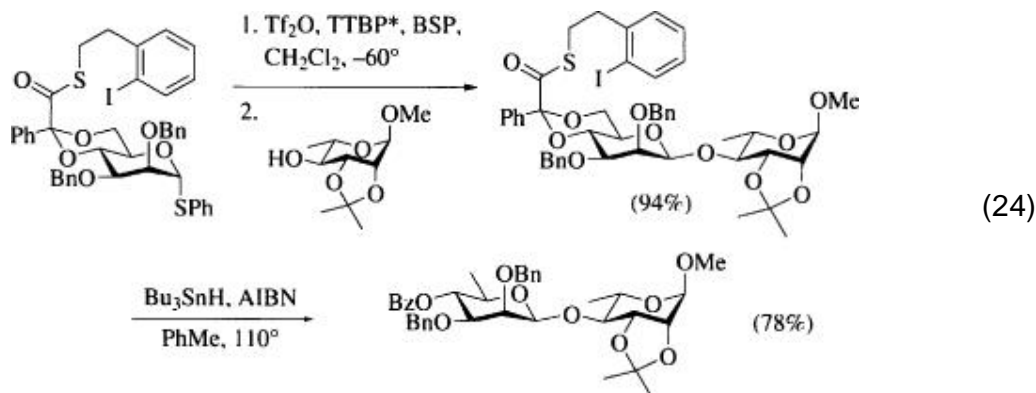


In conjunction with the 4,6-O-benzylidene protecting group, the sulfoxide and

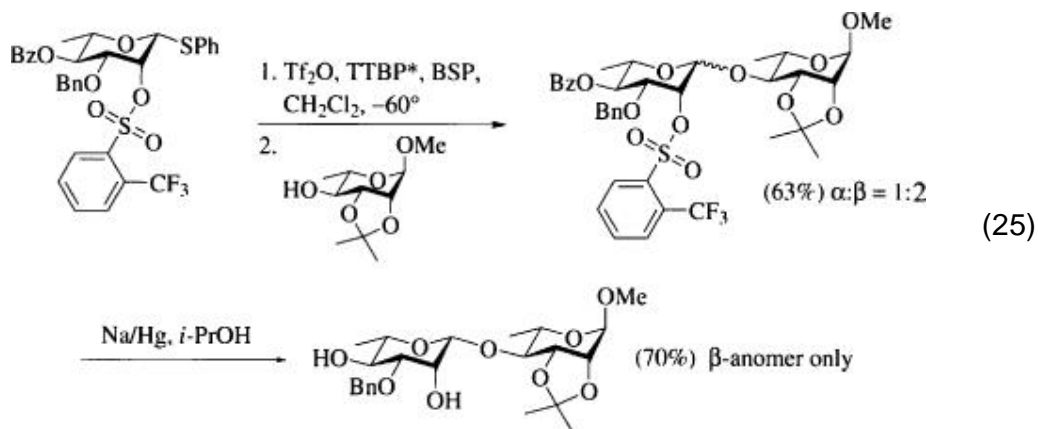
thioglycoside methods are two of the very few (76-81) that permit direct and highly stereoselective formation of the  $\beta$ -mannopyranoside class of glycosidic bond (Eq. 23). (17, 18, 26, 82-84) This subset of glycosidic bonds is not accessible by most methods because of the high  $\alpha$  selectivity imposed by the combination of steric and stereoelectronic factors on the reactions of the mannosyl anomeric oxacarbenium ion. (76, 77) The sulfoxide and thioglycoside methods succeed because the 4,6-O-benzylidene protecting group torsionally disarms and stabilizes the intermediate  $\alpha$ -mannosyl triflate, thereby permitting  $S_N2$ -like displacements to take place. (47) In a rare exception to this rule it has been demonstrated that a 2,3,4,6-tetra-O-benzyl protected  $\alpha$ -S-ethyl mannosyl sulfoxide gives  $\beta$ -selective couplings on activation with iodine in the presence of potassium carbonate. (16) To date, however, only a limited number of examples have been reported and both yields and selectivities are modest. Glycosyl iodides were advanced as putative intermediates in this chemistry. (16)



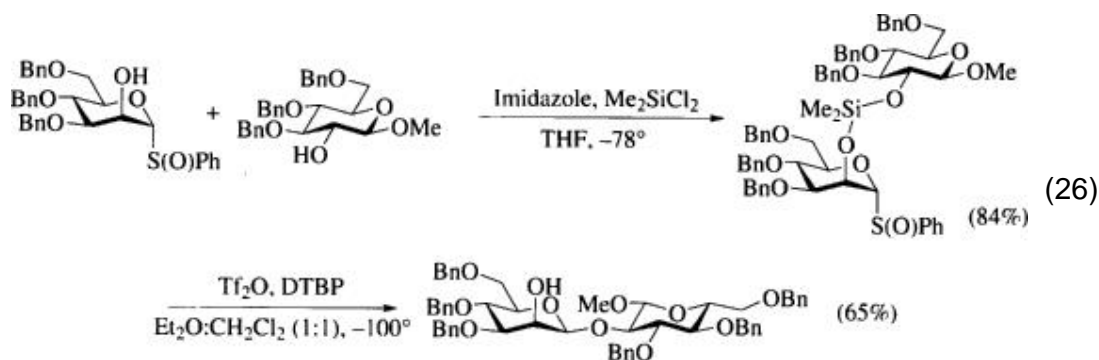
The related  $\beta$ -rhamnopyranosides (6-deoxy- $\beta$ -mannopyranosides) present two distinctly different problems, depending on the enantiomer required. In the D-series, owing to the unavailability of D-rhamnose, itself, the  $\beta$ -glycosides are best accessed by selective deoxygenation of the 6-position of a  $\beta$ -mannoside. This deoxygenation may be achieved in one step by a radical fragmentation of a modified benzylidene acetal, which also serves to control the stereochemistry in the glycosylation reaction (Eq. 24). (85)



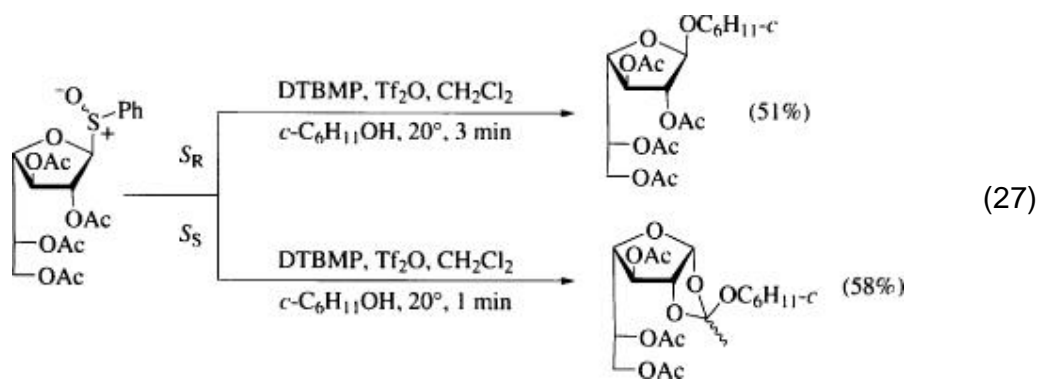
The  $\beta$ -L-rhamnosides are obtained directly by the thioglycoside/sulfinamide method with a rhamnosyl donor carrying the strongly disarming, but non-participating, 2-O-(2-trifluoromethyl)benzenesulfonyl protecting group (Eq. 25). (86) Following glycosylation, the unusual sulfonyl protecting group and the 4-O-benzoyl group are removed with sodium amalgam in 2-propanol. (86)



The synthesis of  $\beta$ -mannosides with complete control of anomeric selectivity has been achieved by intramolecular aglycone delivery. (24, 76, 87-93) In this method the glycosyl acceptor is tethered to the mannose donor by a linker to mannose O-2, and is therefore poised for intramolecular attack of the donor directly on the  $\beta$  face following activation. In one variation on this theme the donor is a sulfoxide and the tether is a silylene group. (24, 89, 93) Initially, tethering of the donor to the acceptor via the silylene group was carried out prior to oxidation of the thioglycoside, (24) but it was subsequently found to be more expedient to conduct the oxidation prior to the tethering reaction (Eq. 26). (89) The ability to form a mixed silylene acetal in high yield in the required manner was ascribed to the slower silylation of the mannose OH as compared to that of the acceptor. A one-pot sequence in which the mannosyl sulfoxide donor with the unprotected 2-OH and the acceptor are mixed in the presence of a potentially bridging lanthanide triflate before activation with triflic anhydride was considerably less selective. (94) No doubt this is due to incomplete tethering and consequent competition from intermolecular reactions. The thioglycoside/sulfinamide method has also been shown to function effectively with 2,3-anhydro-lyxothiofuranosides and 2,3-anhydro-ribothiofuranosides analogously, and with comparable stereoselectivity to the sulfoxide couplings depicted in Eqs. 20 and 21. (72)

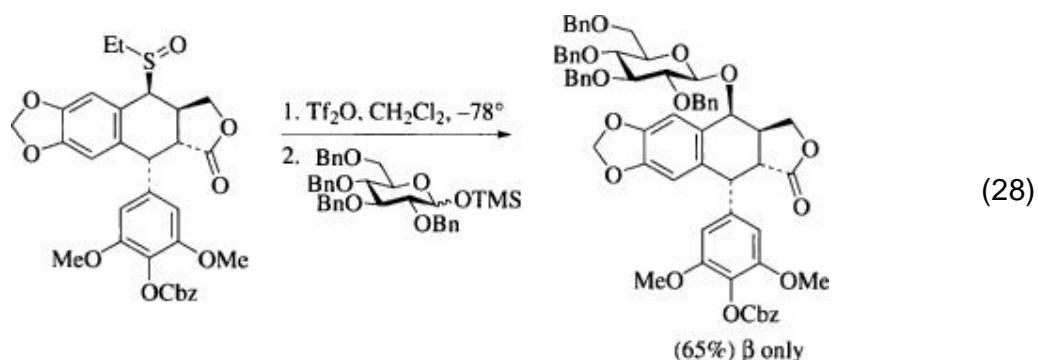


Axial thioglycosides are oxidized predominantly to one sulfoxide, (95-97) and it has been suggested on the basis of X-ray crystallographic studies that the selectivity is the result of the exo-anomeric effect. (96, 98) According to this rationale, one of the lone pairs on sulfur in an axial thioglycoside is positioned underneath the pyranose ring and is therefore sterically shielded whereas the second lone pair is exposed to solvent and so reacts preferentially with most common oxidizing agents. Owing to this stereoselective oxidation, almost all studies on axial glycosyl sulfoxides have been conducted with diastereomerically pure sulfoxides. With equatorial thioglycosides, notwithstanding the exo-anomeric effect, both lone pairs on sulfur are exposed and either can be oxidized. (99-101) The resulting mixture of sulfoxides is not usually separated and is simply used as such in glycosylation reactions on the assumption that there is no significant difference in reactivity. However, there are isolated reports of differing reactivity of glycosyl sulfoxides diastereomeric at sulfur. Thus, it has been reported that the  $S_S$  diastereomer of  $\beta$ -galactopyranosyl phenyl sulfoxide is hydrolyzed twice as quickly as its  $R_S$  diastereomer in 5% aqueous triflic acid at 25°. (102) Perhaps not too surprisingly, a  $\beta$ -galactosidase enzyme discriminates strongly between the same two sulfoxides and only cleaves the  $S_S$  diastereomer. (102) More germane to the glycosylation reaction is the unusual observation that two furanosyl sulfoxides do not react with triflic anhydride at low temperature and show distinctly different reactivity patterns at 0° and above (Eq. 27). (103) No explanation is at present available for this observation.

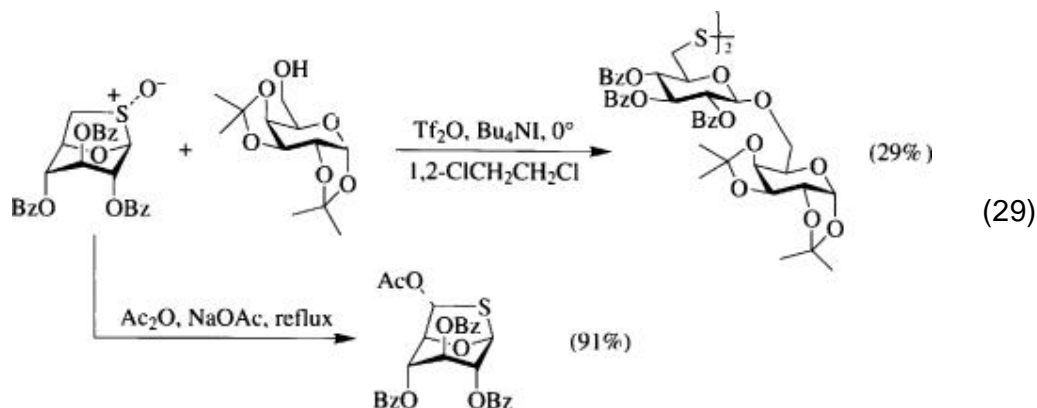


Although the overwhelming majority of sulfoxides employed to date have been of the pyranoside or furanoside classes, acyclic  $\alpha$ -alkoxymethyl sulfoxides can also be employed without undue competition from the Pummerer reaction.

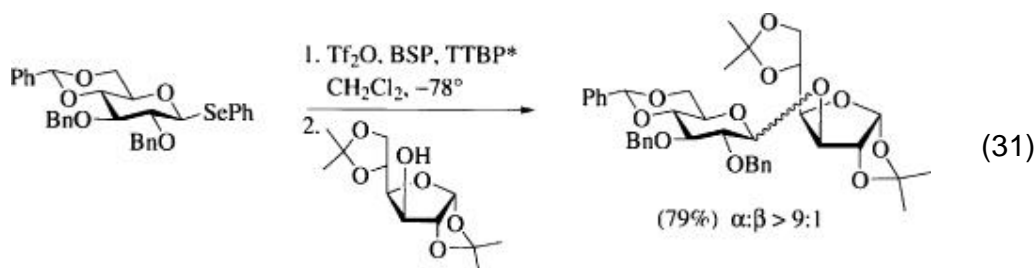
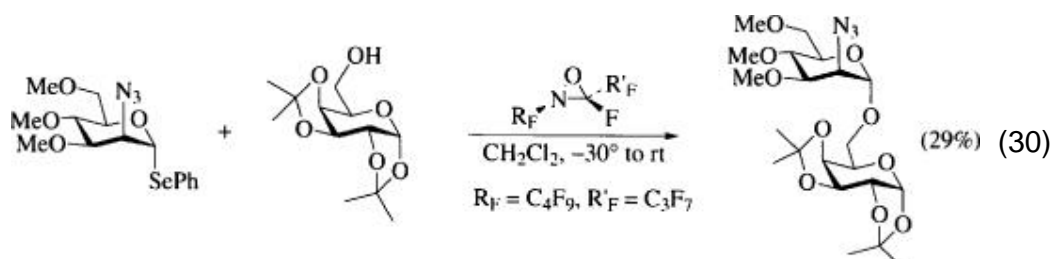
(104) Similarly, an aglycone-based sulfoxide donor has been used in a “reverse-Kahne” glycosylation sequence in the synthesis of podophyllotoxin analogs, again without serious competition from the Pummerer reaction (Eq. 28). (105)



The oxides of 1,6-epithio-  $\beta$ -D-glucopyranose have been briefly investigated as donors in the sulfoxide glycosylation method and found to yield ring-opened glycosylated disulfides (Eq. 29). (106) Upon treatment with acetic anhydride and sodium acetate at higher temperatures, this sulfoxide undergoes Pummerer reaction with introduction of the acetoxy group on the carbon of the bridge, rather than cleavage of the glycosyl-sulfur bond. (106) Protected forms of 5-thioglucopyranosides, as well as 1,5-dithioglucopyranosides, have also been oxidized to the corresponding sulfoxides, whose structures have been determined X-ray crystallographically. (107-110) However, these particular sulfoxides have yet to be employed in glycosylation reactions.

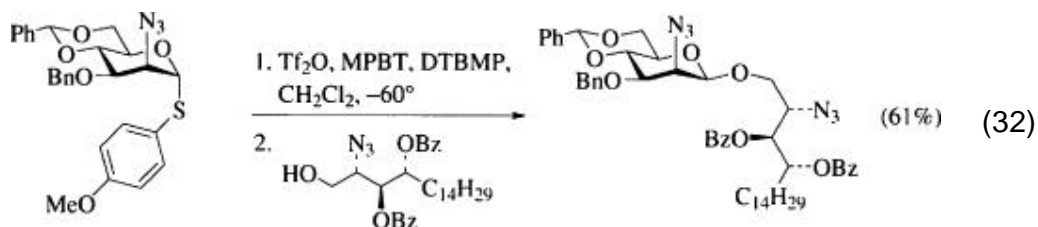


Aryl glycosyl selenoxides, a class of compounds related to glycosyl sulfoxides, are apparently unstable and have to be prepared in situ. With this caveat, their use in glycosylation reactions has been demonstrated. The particular example illustrated (Eq. 30) was reported as giving uniquely the  $\beta$ -mannoside (111) but, in view of the reported (3)  $J_{H,H}$  anomeric coupling of 1.55 Hz, it is far more likely that the glycosylation was  $\alpha$ -selective as depicted. Selenoglycosides are activated for glycosylation by the sulfinate/triflic anhydride method (Eq. 31). (18) The high selectivity for the  $\alpha$ -glucoside, a useful feature of 2,3-di-O-benzyl-4,6-O-benzylidene protected thioglucoside and glycosyl sulfoxide donors, (18, 97, 112) and indeed of other types of 4,6-O-benzylidene protected glucosyl donors, (113) is noteworthy in this example.



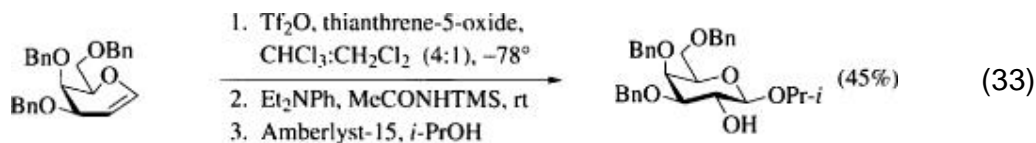


In the thioglycoside method the *S*-phenyl arenethiosulfonates (MPBT), in conjunction with triflic anhydride (the thioglycoside/sulfinate method), only activate armed donors whereas the more potent 1-benzenesulfinyl piperidine (BSP)/triflic anhydride and diphenyl sulfoxide/triflic anhydride combinations (the thioglycoside/sulfinamide and thioglycoside/sulfoxide methods, respectively) activate both armed and disarmed thioglycosides and selenoglycosides. (17-19) However, just as the reactivity of glycosyl aryl sulfoxides toward triflic anhydride can be modulated by the incorporation of electron-donating or electron-withdrawing substituents on the aryl groups, the reactivity of thioglycosides toward the sulfinate/triflic anhydride combinations can be adjusted with substituents on the thioglycoside. Accordingly, it has been demonstrated that neither the *S*-ethyl nor the *S*-phenyl glycosides of 2-azido-2-deoxy-3-*O*-benzyl-4,6-*O*-benzylidene- $\alpha$ -D-thiomannopyranoside are activated by the MPBT/ Tf<sub>2</sub>O combination, presumably due to the strongly disarming azido group, whereas the corresponding, more electron-rich *S*-(4-methoxyphenyl) thioglycoside functions well (Eq. 32). (114) It has also been reported that the *S*-phenyl glycoside of 2-azido-2-deoxy-3-*O*-benzyl-4,6-*O*-benzylidene- $\alpha$ -D-thiomannopyranoside is not activated by the BSP/ Tf<sub>2</sub>O combination whereas the diphenyl sulfoxide/ Tf<sub>2</sub>O protocol promotes smooth  $\beta$ -2-azido-2-deoxy-mannosylation with this donor. (19) Overall, among the three related thioglycoside activating systems described here, the diphenyl sulfoxide/ Tf<sub>2</sub>O combination appears to be the most potent, closely followed by the BSP/ Tf<sub>2</sub>O couple, with the MPBT/ Tf<sub>2</sub>O system being the least reactive and only suitable for armed donors.



In most applications of the oxidative method, the glycol has been protected with arming ether groups but isolated examples are known with esters protecting *O*-4 or *O*-6. (25, 54) It is noteworthy that a 4,6-*O*-isopropylidene group is tolerated as is the use of a uronate-glycol with its more highly oxidized, electron-withdrawing carboxylate substituent. (25) Most examples have been conducted with *D*-arabino glycols, which lead ultimately to the gluco or manno configured sugars. A reaction of *D*-lyxo glycol, affording a galacto product has also been successfully carried out (Eq. 33). (57) What remains unknown at this

time is the effect of a pseudo-axial group at position 3 of the glycal, as in the ribo glycals, on the stereochemical outcome of these reactions.



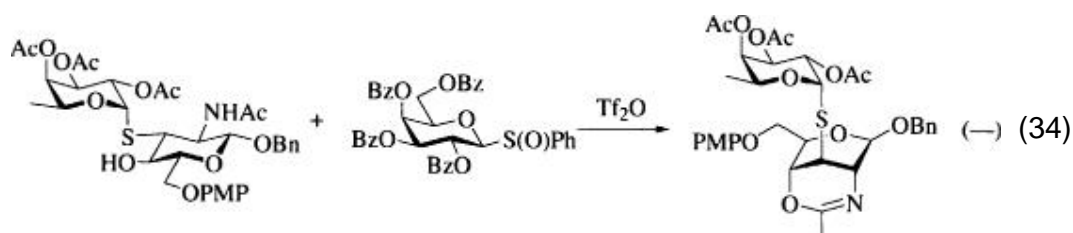
### 3.2. Acceptors

An attractive feature of the sulfoxide method is the ability to couple to even the most hindered of alcohols. Thus, for example, it was demonstrated that the highly congested axial 7  $\alpha$  -hydroxy group of the cholanic acid series was readily glycosylated via the sulfoxide method (Eq. 1). (9) A comparable double glycosylation of a closely related 7  $\alpha$  -, 12  $\alpha$  -steroidal diol, using tetra-*O*-benzyl-  $\beta$  -D-glycopyranosyl phenyl sulfoxide was carried out on the scale of 1 mole. The double  $\alpha$  -glucoside was isolated in 45% yield, thereby demonstrating the potential of the method for large-scale synthesis of hindered glycosides. (115) The glycosylation of somewhat hindered tertiary alcohols has been achieved by the sulfoxide method in high yield. (84, 116) The nucleophilicity of hindered alcohols or phenols can be enhanced by their conversion into tributylstannyl ethers. (65, 117-119) The very weakly nucleophilic dialkylphosphoric acids, in the form of their tetrabutylammonium salts, have been successfully glycosylated by the sulfoxide method. (120, 121) In this manner the successful synthesis of antigenic  $\beta$  -mannosyl phosphoisoprenoids was achieved for the first time. (120, 121)

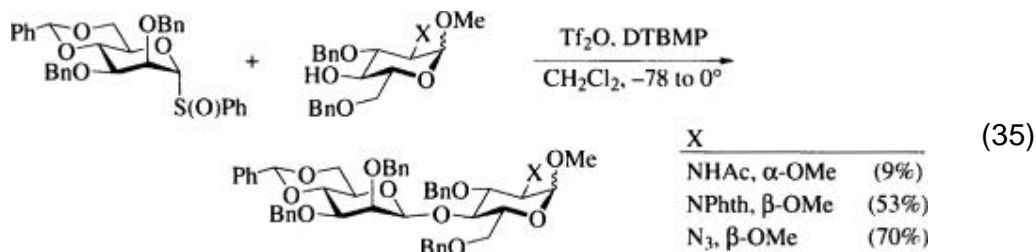
As the thioglycoside method affords the same intermediate glycosyl triflates as the sulfoxide method it is reasonable to assume that once the initial activation has taken place the scope and limitations in terms of acceptors and solvents are very comparable. Accordingly a full range of primary, secondary, and tertiary glycosyl alcohols have been found to be glycosylated in high yield by this method. (17-19) The dehydrative glycosylation method has also been found to be successful for the glycosylation of a range of primary, secondary, and tertiary alcohols. (20, 21) It has been satisfactorily applied to the glycosylation of carboxylic acids and also of phosphoric acids. (20, 21) The scope of the glycal method is considerable and a wide range of primary and secondary alcohols have performed successfully as glycosyl acceptors. (23, 25, 54, 57) In addition, couplings have been performed in good yield with *tert*-butyl alcohol (23) and with phenol. (23)

As with all types of glycosyl donors, (122) coupling to the 4-OH of *N*-acetylglucosamine derivatives is problematic in the sulfoxide and

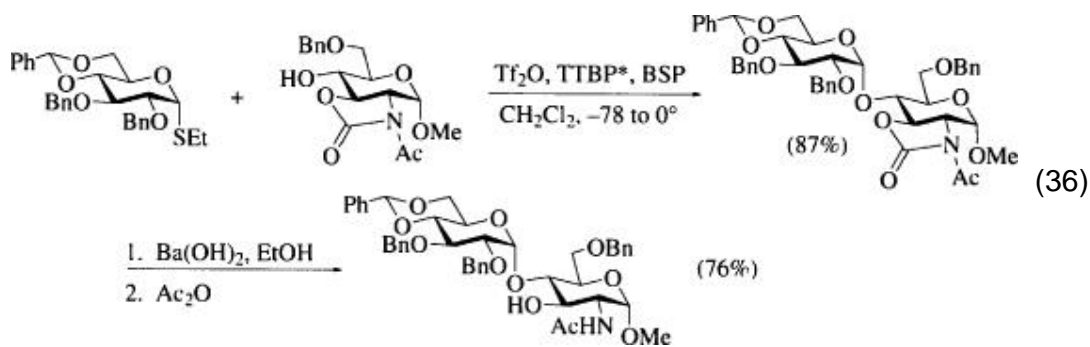
thioglycoside methods and, presumably, in the dehydrative protocols. The lack of nucleophilic character of these alcohols may be due to the formation of cyclic oxazines following triflation of the amide (Eq. 34). (123) It should, however, be possible to eliminate this problem by preactivation of the sulfoxide with triflic anhydride before addition of the acceptor. Moreover, the formation of this type of byproduct accounts neither for the poor reactivity in most other glycosylation methods, nor for the reports of failed glycosylations with acceptors bearing amido groups much further removed from the nucleophilic alcohol. (124) Intermolecular nucleophilic attack of the amide on the glycosyl donor leading to the formation of a glycosyl imidate has also been demonstrated in other types of coupling reactions. (125) Alternatively, it has been suggested that the underlying lack of reactivity of this particular type of alcohol may arise from intermolecular hydrogen bonding of the amide group which effectively increases steric hindrance about the alcohol. (52)



Whatever the reason for the lack of reactivity, the usual surrogates for the acetamido group, namely the phthalimido or azido groups, provide effective acceptors. A comparative study, conducted for sulfoxide mediated  $\beta$ -mannosylation, concluded that the azide derivative was the most effective acceptor (Eq. 35). (52) A chitobiose derivative in which both amino groups were protected as sulfonamides has also been successfully employed as a glycosyl acceptor in a synthesis of the common core pentasaccharide of the N-linked glycoproteins by the sulfoxide method. (126) This suggests that sulfonamides in general may provide an alternative means of protecting amines that is compatible with the sulfoxide and, most likely, the thioglycoside and dehydrative coupling methods.

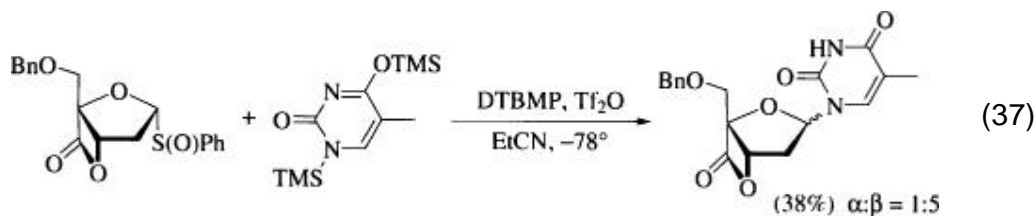


An alternative solution to the *N*-acetylglucosamine 4-OH problem, employed in conjunction with the thioglycoside method, is the use of an oxazolidinone protected *N*-acetyl glucosamine acceptor (Eq. 36). (127) This glucosamine derivative proved to be a convenient and reactive acceptor toward a number of thioglycoside donors. It was suggested that the high reactivity is related to the cyclic protecting group which reduces the degree of steric hindrance around the nucleophilic alcohol. (127)



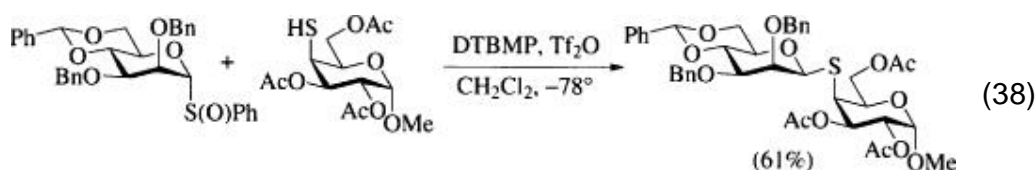
### 3.3. *N*-Glycosides and Nucleosides

Certain types of nitrogen nucleophiles are also compatible with the sulfoxide method. Thus, persilylated pyrimidine bases can be used, leading to the formation of nucleosides (Eq. 37). (73, 128, 129) It has also been demonstrated that *N*-trimethylsilylacetamide functions as an acetamide surrogate, and is a suitable *N*-nucleophile in the sulfoxide method. (9) 4-Fluoroaniline has also been used successfully as a nitrogen-based nucleophile in a so-called “reverse-Kahne” sequence in which a benzylic sulfoxide was used as a synthon for a benzylic cation. (105) The use of more basic nucleophiles would appear to be problematic owing to the liberation of triflic acid in the course of the reaction. Silylated nitrogen nucleophiles have also been used successfully in the dehydrative method. (20, 21) As yet there are no reported examples of the use of nitrogen based nucleophiles in either the thioglycoside/sulfinate or oxidative methods. Sodium azide may be used as acceptor in the dehydrative (21) and oxidative (58) methods leading to the formation of glycosyl azides.



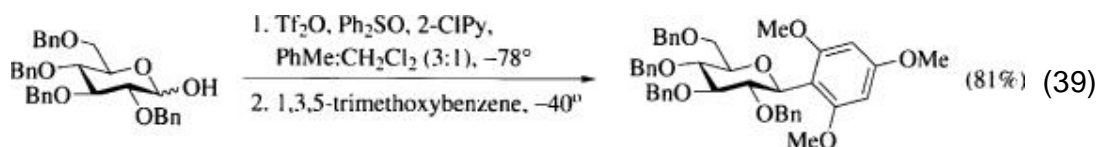
### 3.4. Thioglycosides

The successful use of thiols as nucleophiles, leading to thioglycosides, has been reported in both the sulfoxide (Eq. 38) (130) and dehydrative methods, (20, 21) but not yet for thioglycoside and oxidative methods. To date, all examples of the use of thiols as acceptors in these glycosylation reactions employ armed donors, but there is no reason to suspect that they should not function equally well with disarmed donors.



### 3.5. C-Glycosides

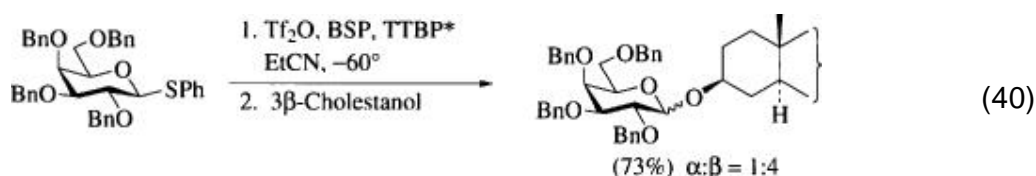
In contrast to the sulfoxide, thioglycoside, and oxidative methods, the dehydrative method has been demonstrated to enable the formation of C-aryl glycosides when electron-rich aromatics are used as nucleophiles (Eq. 39). (20, 21) The recent report of the coupling of a benzyl ethyl sulfoxide with allyltrimethylsilane, (105) under typical sulfoxide glycosylation conditions, however, suggests that C-glycoside formation may yet be possible with a broader range of nucleophiles in these glycosylating systems.



### 3.6. Solvents

A wide range of solvents is acceptable, including toluene, dichloromethane, ether, ethyl acetate, and propionitrile, with the last being preferred over acetonitrile because its lower freezing point is more compatible with the usual

reaction conditions. When selecting a solvent, however, the potential to influence the equilibrium between covalent intermediates, for example glycosyl triflates, contact ion pairs, and solvent-separated and free ions must not be overlooked: in the absence of neighboring group participation, the solvent choice can have a drastic effect on stereoselectivity. A particularly marked solvent effect is the stereodirecting nitrile effect, in which the solvent attacks the activated glycosyl donor to provide an  $\alpha$ -nitrilium ion. (131, 132) This enables equatorial glycosides to be obtained even with arming O-2 protecting groups, such as benzyl ethers, when propionitrile is used as solvent (Eq. 40). (9, 18) In the example depicted in Eq. 40 a 1:1 mixture of anomers was obtained when the glycosylation was conducted in the absence of propionitrile but otherwise under identical conditions. (18)

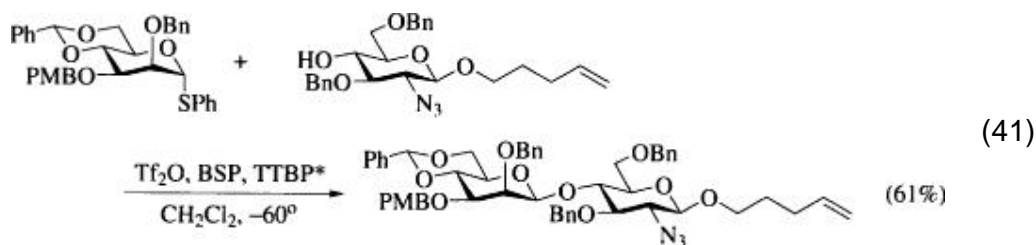


### 3.7. Functional Group Compatibility

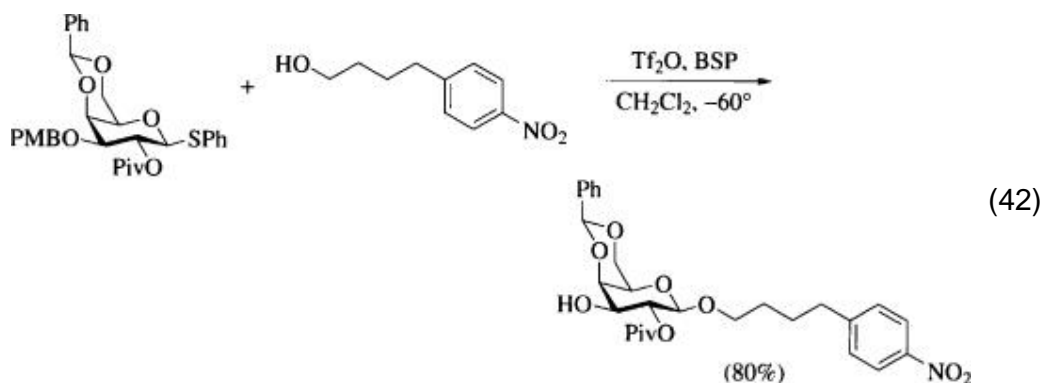
All four methods described in this chapter show excellent compatibility with esters, the more robust silyl ethers, and standard acetals, as well as bis(acetal) protecting groups. (133) Alkyl azides are tolerated as are phthalimides but there obviously remains a question with respect to amides and carbamates whether adjacent (Eq. 34) (52) or remote (124) from the site of reactivity. Nevertheless, there are examples of successful sulfoxide couplings to acceptors carrying remote peptide bonds (64, 65) as well as with donors bound to a resin via an amide linkage. (74, 134) Tertiary amides lacking the N-H bond are well tolerated. (52) Sulfonamides appear to be tolerated although examples are as yet very limited. (126)

In all four methods there is obviously the compatibility issue of multiple bonds and electron-rich aromatic systems given the highly electrophilic nature of the activating species employed. Thus, the very essence of the glycol method is the reaction of an enol ether, the glycol, with an activated sulfoxide. Other such electron rich alkenes, serving as protecting groups for donors or as integral components of donors are unlikely to be compatible with any of the methods described here. However, it has been demonstrated that even in the glycol method, the glycol functionality is permissible in the acceptor. Careful control of the stoichiometry of the activating reagents is presumably necessary in these cases. (54, 57) Both methyl propiolate and 4-allyl-1,2-dimethoxybenzene have been included in sulfoxide glycosylations

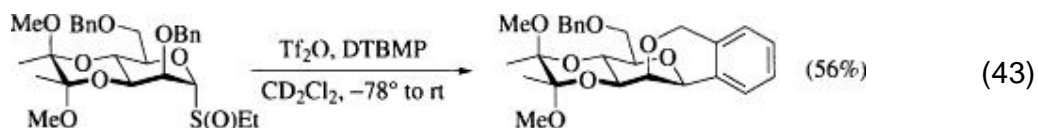
as scavengers of sulfonyl triflates. (11, 70) However, provided that caution is exercised when either reaction partner contains a simple multiple bond, the presence of unsaturation is tolerated in the donor or acceptor. Thus, it has been demonstrated that in  $\beta$ -mannosylation by the sulfoxide method, allyl ethers, common carbohydrate protecting groups, (135, 136) are tolerated at both the 2- and 3-positions of the donor. (84) It has also been shown that acceptors containing pentenyl glycosides may be employed in both the sulfoxide and thioglycoside/sulfinate methods (Eq. 41). (137) Propargyl alcohol has been successfully used as acceptor in the thioglycoside/sulfinate method, (138) and allyl alcohol functions as a standard acceptor alcohol in the glycal method. (25, 54)



Although trimethoxybenzene has been used as nucleophile in the formation of C-aryl glycosides by the dehydrative glycosylation method (Eq. 39), the compatibility of other electron-rich aromatics is an important issue. Provided that the sulfoxide glycosylation reaction is conducted under the standard conditions in the presence of a hindered non-nucleophilic base, *p*-methoxybenzyl ethers, even on O-2 of the donor, are fully compatible. (116, 139) Similarly, *p*-methoxybenzyl ether protected glycals function effectively as donors in the glycal method. (23) *p*-Methoxybenzylidene groups are also compatible with the sulfoxide method, provided that care is taken to ensure sufficient base is present to buffer the acid generated in the course of the reaction. (139) On the other hand, when the base is excluded in order to avoid the formation of orthoesters, *p*-methoxybenzyl ethers may be cleaved. Nevertheless, it should be noted that triflic acid is not liberated in any of these glycosylation reactions until the addition of the acceptor and coupling. Thus, provided that acid-labile protecting groups do not interfere with the actual activation, *p*-methoxybenzyl ethers or *p*-methoxybenzylidene acetals should be compatible with glycosylation. They should only be cleaved after the coupling if the base is omitted, as was the case in the thioglycoside/sulfonamide coupling depicted in Eq. 42. (66)



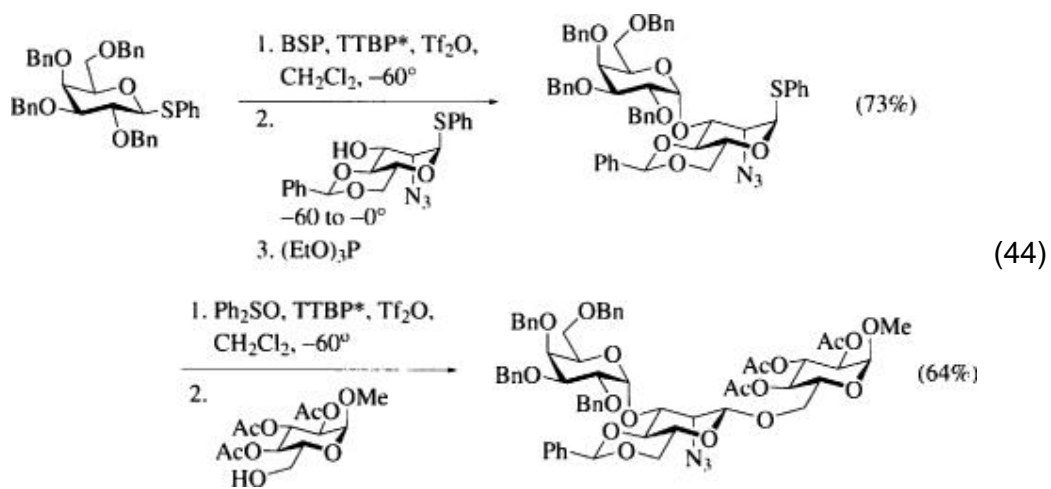
Benzyl ethers are fully compatible with any of the four methods. The only documented case of a side reaction with a benzyl ether (Eq. 43) involved this functional group engaging in an intramolecular Friedel-Crafts reaction. A 2-O-benzyl ether of a donor was observed to attack the anomeric position (VT NMR experiment) when the intermediate glycosyl triflate was warmed above 5°, (140) Benzylidene acetals have so far been found to be compatible with the sulfoxide and thioglycoside/sulfinate methods and it is likely that they are similarly stable to the conditions employed in the dehydrative and glycal methods. One exception to this rule is the reported cleavage of a benzylidene acetal in a sulfoxide donor when iodine was used as the promoter. (16)



The judicious use of scavengers of sulfenic acids and sulfenyl triflates such as methyl propiolate and trimethyl and triethyl phosphite can protect thioglycoside functionality in the acceptor alcohol against premature activation in both the sulfoxide (10-12, 141) and thioglycoside methods. (19) This leads to a considerable shortening of oligosaccharide syntheses as is evident from Eqs. 22 (11) and 44. (19) The synthesis depicted in Eq. 44 is also noteworthy for the highly stereoselective formation of a  $\beta$ -glycosidic bond to a mannosamine, which takes advantage of the directing ability of the 4,6-O-benzylidene protecting group. Highly deactivated phenyl thioglycosides, such as those bearing the strongly electron-withdrawing 2-azido-2-deoxy functionality, survive the sulfoxide (99) and thioglycoside (19, 114) coupling methods even in the absence of scavengers. In one such example S-phenyl 2-azido-4,6-O-benzylidene-2-deoxy- $\alpha$ -D-thioglycoside was successfully

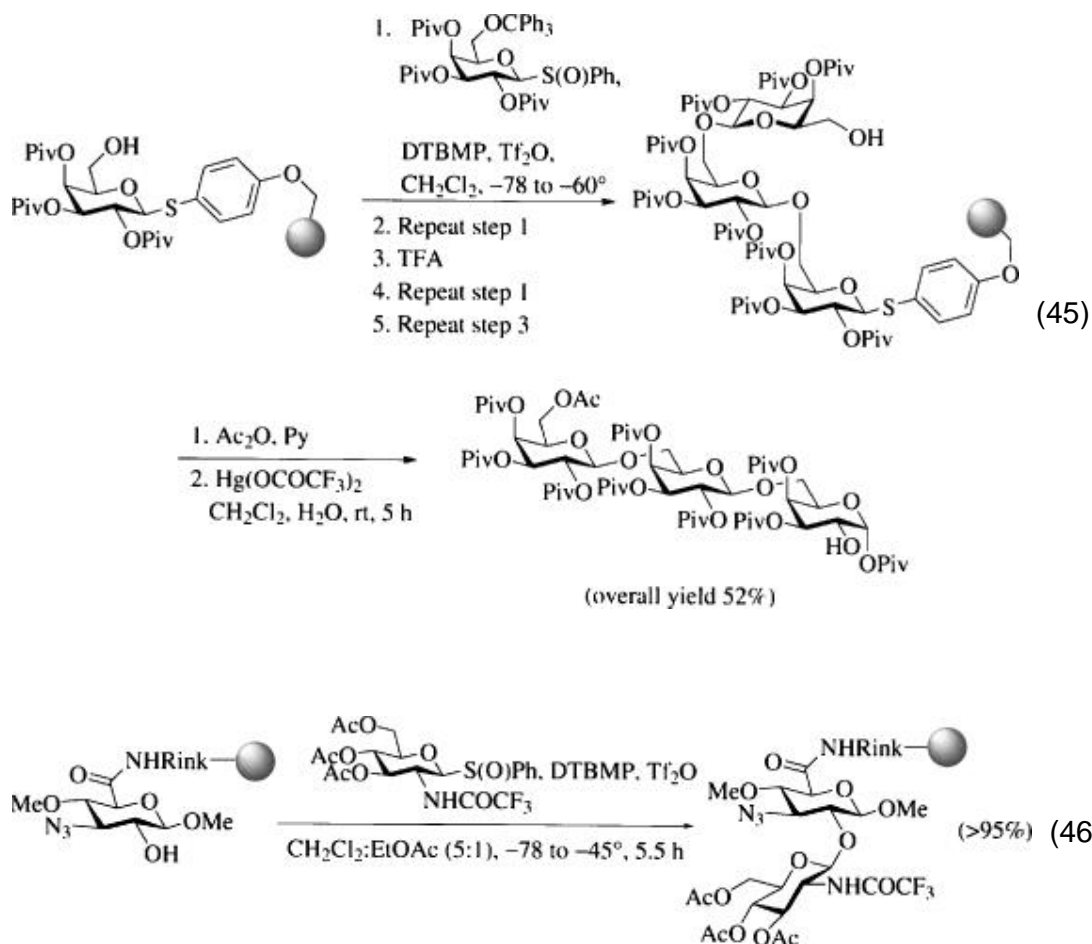


coupled to a galactosyl sulfoxide in high yield in the absence of any scavenger excepting the base DTBMP. (99)



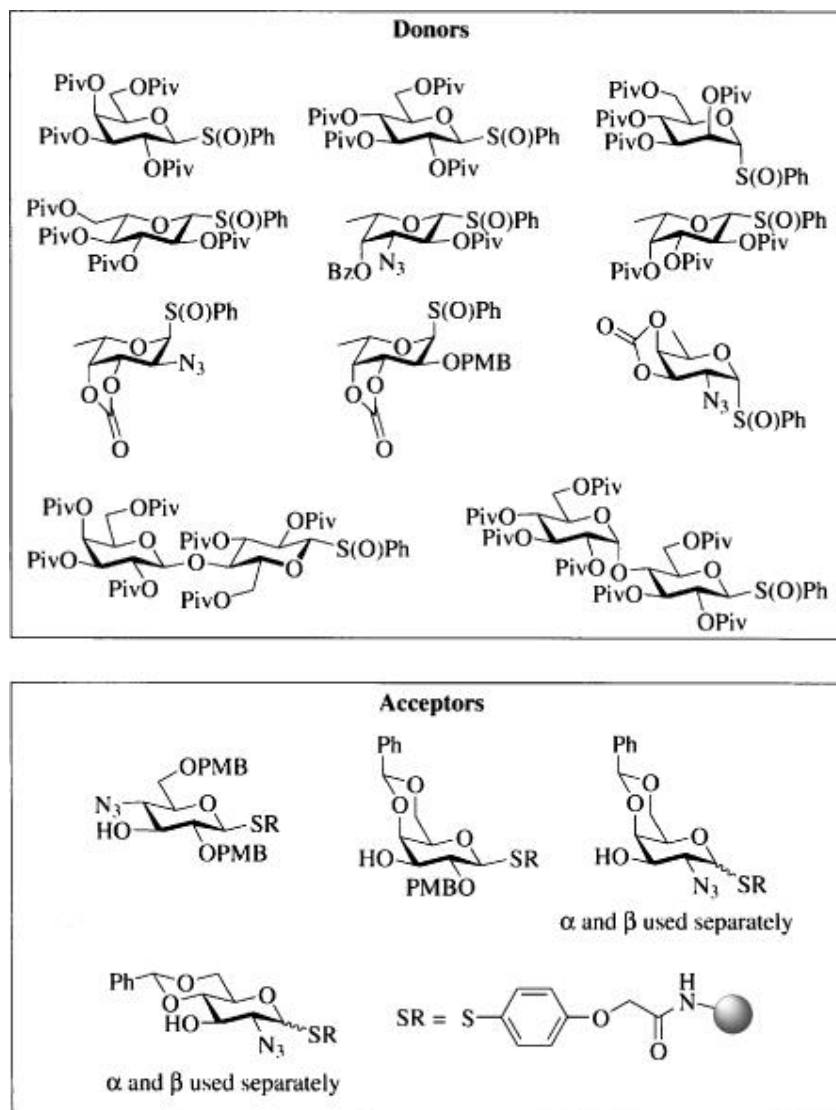
## 4. Polymer-Supported Glycosidic Bond Formation

The potential of polymer-supported methods in the synthesis of oligosaccharides is widely recognized but it is only within the last decade that the field has blossomed following the advent of more powerful, predictable glycosylation reactions. (142) The sulfoxide method is ideally suited to polymer-supported oligosaccharide synthesis following an acceptor-bound strategy. This is largely because of the highly reactive nature of the intermediates, which helps overcome the rate decrease most solid-supported reactions exhibit relative to the corresponding homogeneous reactions. This potential was realized in 1994 (143) and was soon exploited for the preparation of a combinatorial library of di- and trisaccharides. (74) The area has been reviewed recently. (144) The initial research is summarized in the scheme shown in Eq. 45. The primary alcohol acceptor was bound to the standard Merrifield cross-linked polystyrene resin by a thioglycoside linker. (143) A galactosyl sulfoxide was used as donor and triflic anhydride as activator in the presence of DTBMP as base. In order to ensure a good yield, a second treatment of the resin with the sulfoxide/triflic anhydride/DTBMP was employed. The trityl protecting group was then removed from the disaccharide and the coupling sequence repeated to give the resin-bound trisaccharide. Release from the resin with mercuric trifluoroacetate provided the soluble protected trisaccharide in 52% overall yield. The migration of the pivaloyl group to the anomeric position at the reducing end of the chain reveals the role of neighboring group participation in this particular deprotection. On the basis of independent experiments that showed the yield of the resin cleavage step to be 70–75%, it was estimated that each of the steps carried out on resin-bound substrates, including glycosylation, proceeded with an average yield of 94–95%. Both axial and equatorial glycosidic linkages to typical carbohydrate secondary alcohols were also forged in high yield by this general strategy, with the stereoselectivity being a function of the armed or disarmed nature of the donor in full agreement with corresponding solution-phase couplings. (143) A later study employed a glucuronic acid based acceptor immobilized on Rink Amide resin (Eq. 46). (134, 145)



The parallel synthesis of an approximately 1300-member combinatorial disaccharide library has been achieved by the coupling of a series of six resin-bound acceptors to twelve sulfoxide donors. The support employed was the Tentagel resin with attachment via a functionalized phenylthioglycoside. The split and pool technique was used to assemble the library. (74) The various resin-bound acceptors and the sulfoxides employed in this study are shown in Figure 1. After two glycosylation steps any azides present were reduced to amines, which were in turn acylated, again combinatorially, with a series of fifteen diverse acylating agents. Removal of the protecting groups afforded the resin bound library that was screened for binding to *Bauhinia purpurea* lectin. In this manner two Tentagel-bound ligands with a higher affinity for the lectin than the comparable immobilized natural one were identified.

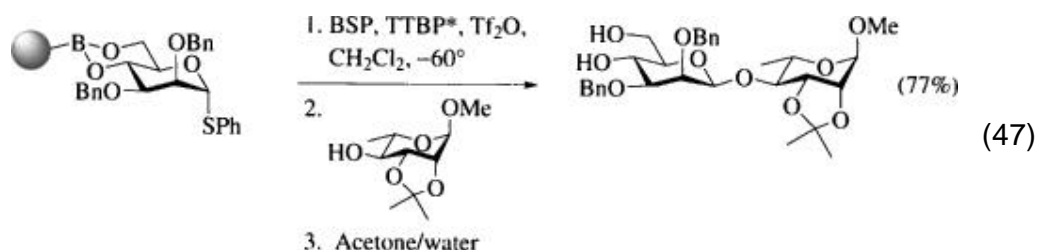
**Figure 1.**



The sulfoxide method has also been used in polymer-supported solution phase synthesis. A substituted 9-fluorenylmethanol was attached to aminoethylated polyethylene glycol (PEG) via a succinoyl linker. Two glycosylation reactions were carried out using the sulfoxide method with triflic anhydride in dichloromethane in the presence of DTBP as base. The disaccharide was released from the linker on treatment with triethylamine in dichloromethane. Unfortunately, the temperature at which these couplings were conducted was not reported although the reaction time was given as 16 hours. (146) Although the soluble polymer-supported approach is an attractive one, in principle because of the similar reactivity profile to standard solution phase reactions, the solubility of PEG in dichloromethane at low temperatures is questionable, and may limit extension of this method to the full range of

glycosylations possible with the sulfoxide method.

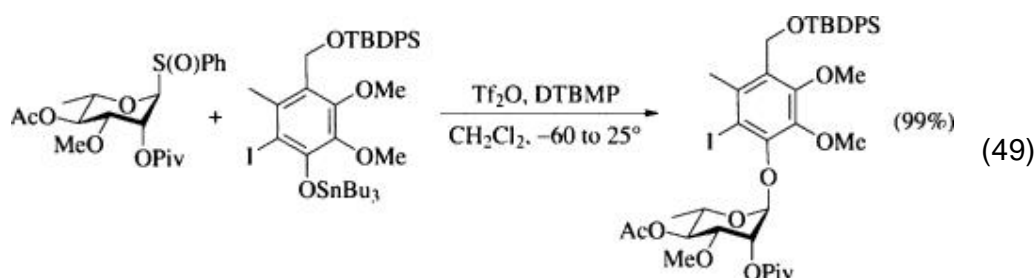
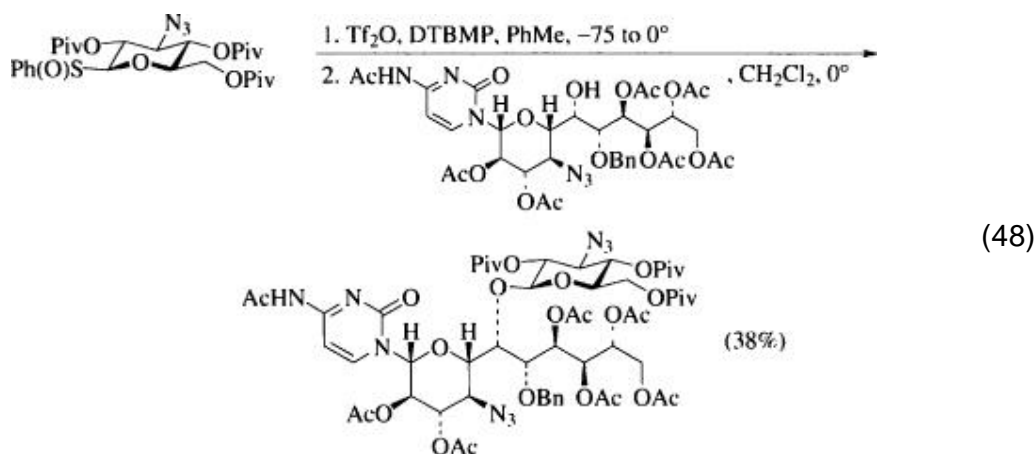
When preformation of a glycosyl triflate prior to mixing with a glycosyl acceptor is required, as in the  $\beta$ -mannosylation reaction, an acceptor-bound strategy is not practical because of the need to manipulate cold solutions of thermally and hydrolytically unstable glycosyl triflates. A donor-bound approach is therefore preferred in such cases. For implementation of this strategy with glycosyl sulfoxides, oxidation of the thioglycoside to the sulfoxide on resin remains the problem, although a recent description of controlled, polymer-supported sulfoxide formation employing hydrogen peroxide with catalysis by scandium triflate may provide a solution. (147) This situation may be averted if the thioglycoside is oxidized to the sulfoxide prior to attachment to the resin. (148) Alternatively, the thioglycoside itself may be used as a donor with activation initiated by the benzenesulfinyl piperidine/triflic anhydride combination, when the question of oxidation to the sulfoxide is eliminated. Such a system (Eq. 47) has been successfully employed for the synthesis of  $\beta$ -mannosides with the donor bound to the polystyrene support by means of a 4,6-O-polystyryl boronate ester. (149)



Automated oligosaccharide synthesis, despite remarkable advances, (150) is a field that is still very much in its infancy. Nevertheless, the sulfoxide, thioglycoside/sulfinylate, and dehydrative methods with their high reactivity and broad generality have considerable potential as means by which successive glycosylations may be accomplished. Instrumentation must be suitably engineered to operate at the low temperatures typically required by these methods.

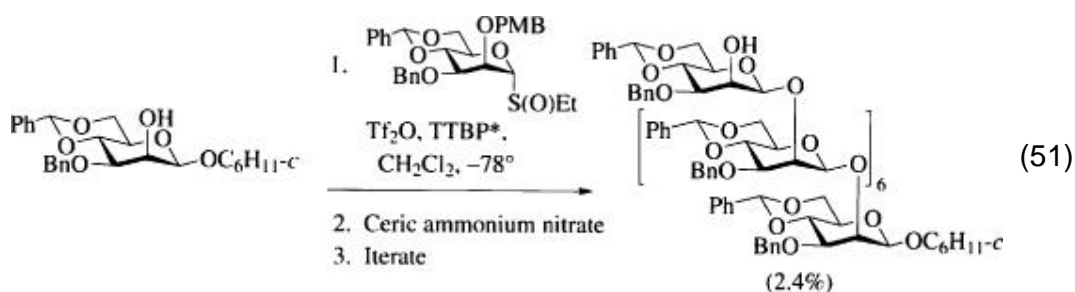
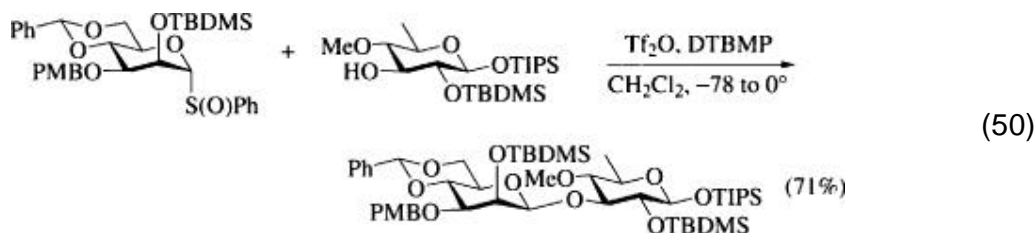
## 5. Applications to Synthesis

Application of the sulfoxide method to the synthesis of numerous natural products, involving the glycosylation of a wide variety of hindered unreactive alcohols, serves to illustrate both the power of the method and the mildness of the glycosylation conditions that tolerate sensitive functionality. A widely cited example is the one-pot synthesis of the ciclamycin O trisaccharide discussed above (Eq. 22). (11, 70) Other early applications include the synthesis of hikizimycin (Eq. 48), (151) wherein it was reported that several other glycosylation methods failed to give the desired saccharide, and the glycosylation of a hindered phenol in a synthesis of the calicheamicin oligosaccharide (Eq. 49). (117) This latter coupling is also noteworthy for its use of the tributylstannylated phenol, with its improved nucleophilicity, as opposed to a simple phenol as acceptor.

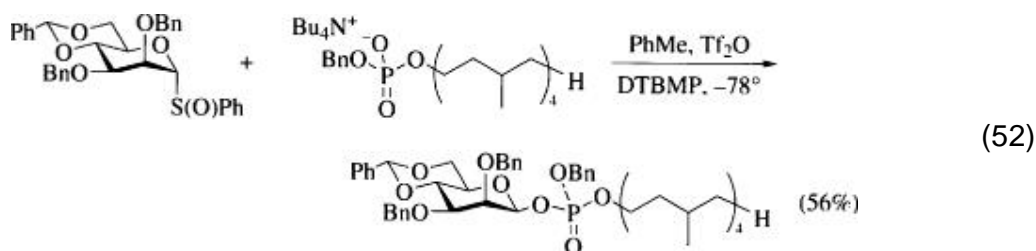


A major success of the sulfoxide method has been the ability to synthesize directly the  $\beta$ -mannopyranosides, with excellent yield and stereoselectivity. (82-84) This is nicely illustrated in the synthesis of everninomycin 13,384-1 (Eq. 50), (152) and in the syntheses of two  $\beta$ -mannans, one of which is shown

in Eq. 51. In this example, iterative application of the sulfoxide method affords an octasaccharide in which each linkage is a  $\beta$ -mannopyranoside. (139) Previously, the longest mannan of this type obtained by indirect methods was the hexasaccharide; (153) the octasaccharide has since also been obtained by indirect methods. (154)

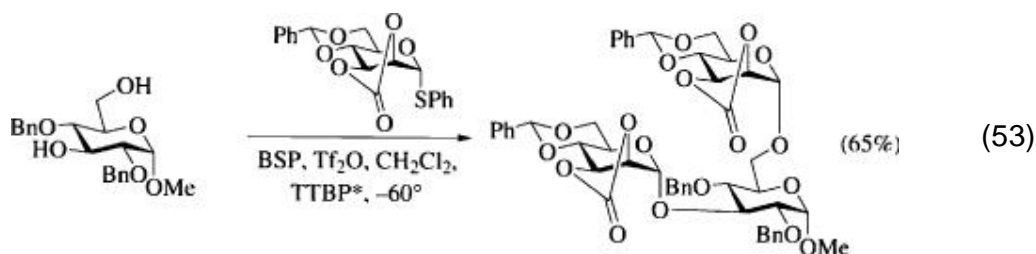


The power of the sulfoxide  $\beta$ -mannosylation protocol is very well illustrated by the synthesis of a  $\beta$ -mannosyl phosphoisoprenoid (Eq. 52), a member of a class of compounds known to be very difficult to access stereoselectively. (120, 121)



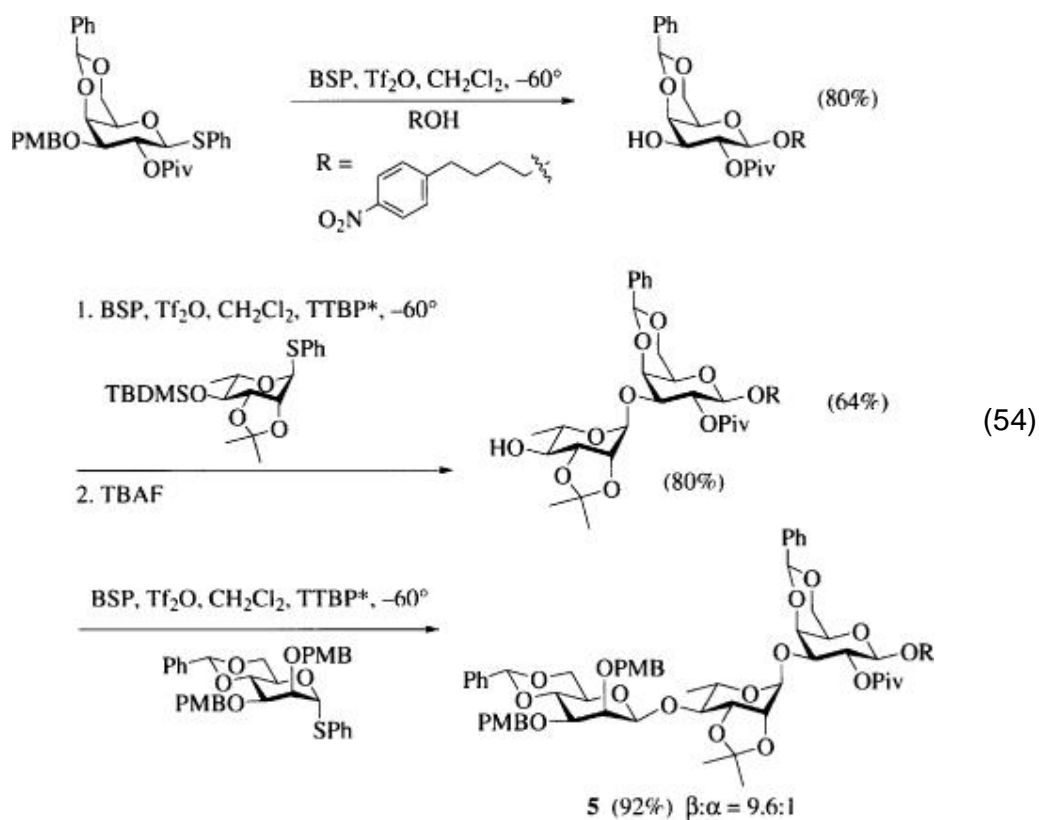
The thioglycoside/sulfinamide method, when employed with the potent 1-benzenesulfinylpiperidine promoter, has been used to effect a one-pot double glycosylation of a mannoside 3,6-diol resulting in a simple

synthesis of the concanavalin A trisaccharide binding unit (Eq. 53). (18) In this synthesis the very high  $\alpha$ -selectivity (140) of the 4,6-O-benzylidene-2,3-O-carbonylmannosyl donor is noteworthy in light of the usual  $\beta$ -directing effect of the 4,6-O-benzylidene group in mannosylation by the sulfoxide and thioglycoside/sulfinate methods. (18) It has been suggested that the strong  $\alpha$ -directing effect of the 2,3-O-carbonate in this chemistry, which contrasts with the known  $\beta$ -directing effect of the same group in mannosylation by the insoluble silver salt method, (155) arises from the imposition of a half-chair conformation on the intermediate mannosyl triflate, which facilitates ionization to the oxacarbenium ion. (140) The 2,3-O-carbonate and 2,3-O-acetonide protecting groups are similarly highly  $\alpha$ -directing in the rhamnopyranoside series by either the thioglycoside/sulfonamide (66) or the thioglycoside/sulfoxide methods, (19) whereas they are  $\beta$ -directing by the insoluble silver salt method. (156, 157) In the insoluble silver salt method glycosyl bromides, not triflates, are employed and these are much less readily ionized, thereby counteracting the effect of the 2,3-O-carbonate.

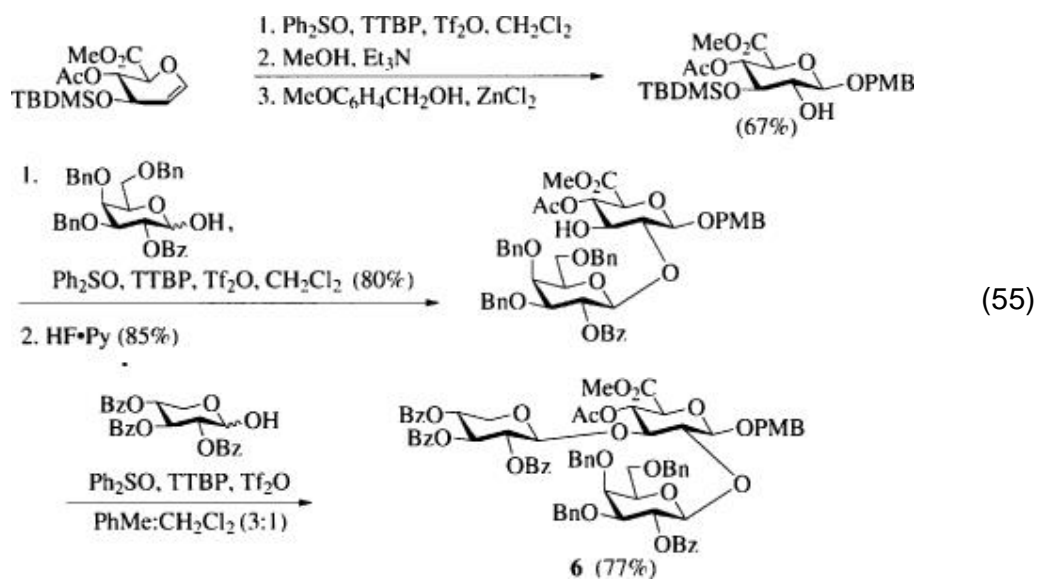


The synthesis of a Salmonella type E<sub>1</sub> core trisaccharide analog illustrates the generality of the thioglycoside/sulfinate method using 1-benzenesulfinylpiperidine (Eq. 54). (66) The target compound 5 contains three of the four main classes of glycosidic bond (equatorial cis-1,2; equatorial trans-1,2; and axial trans-1,2), all of which are synthesized in high yield using the same reagent combination. The base is omitted in the conditions for the formation of the  $\beta$ -galactosidic bond to avoid orthoester formation.



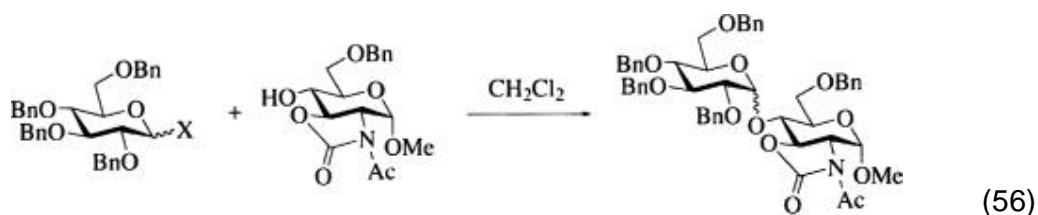


A combination of the glycal and dehydrative methods was used to assemble a trisaccharide fragment **6** of the potent immunologic adjuvant QS-21A (Eq. 55). (25)



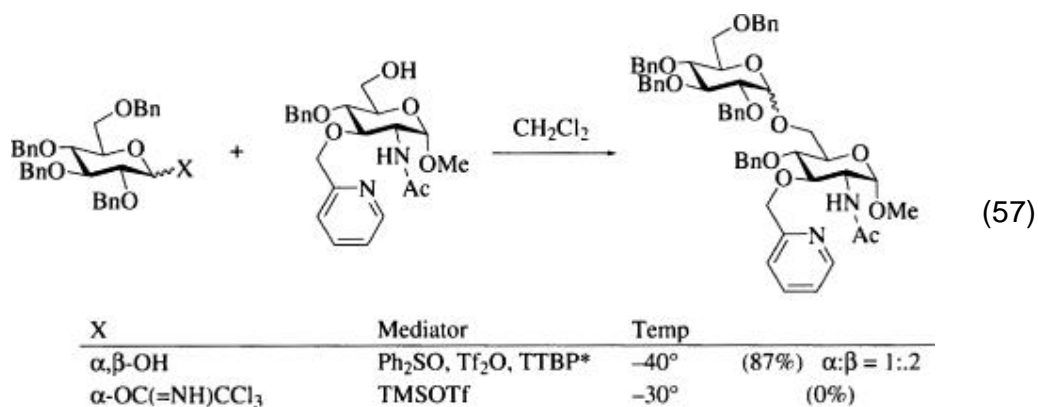
## 6. Comparison with Other Methods

There exists a plethora of methods for the formation of glycosidic bonds. This is testimony to the continuing, even increasing importance of the problem and to the inability of any one method to meet the considerable challenge of the high-yield, stereocontrolled synthesis of more than a select few classes of linkage. Problems associated with the use of toxic mediators, the disposal of heavy-metal byproducts, and the instability of other promoters and/or donors have resulted in only a relatively small selection of these methods finding common usage in modern oligosaccharide chemistry. Analysis of a compilation (158) of the more than 700 glycosylations published in the year 1994, when most of the major glycosylation reactions were in place, reveals that three methods, namely the use of glycosyl bromides or chlorides, glycosyl imidates, and thioglycosides as donors, far outstrip all others in popularity. The use of glycosyl bromides or chlorides as donors has been reviewed recently, (159) as have the trichloroacetimidate (160-163) and thioglycoside methods. (164-166) Other popular methods reviewed in recent years include the use of glycosyl fluorides (167, 168) and glycosyl phosphites (169, 170) as donors, as well as that of pentenyl glycosides (171-173) and of glycals. (56, 174-178) Numerous other glycosylation methods are reviewed in one or more of several books to appear in recent years covering the general area of glycosylation. (5, 179-181) Unfortunately, despite the enormous amount of literature on each of the main glycosylation methods, detailed studies comparing one method accurately to another are extremely limited. One study, however, did compare the sulfoxide, thioglycoside, dehydrative, and trichloroacetimidate methods for glycosylation of a glucosamine 4-OH derivative (Eq. 56). (127) In this particular glycosylation the sulfoxide and dehydrative methods are somewhat more stereoselective, but the thioglycoside and trichloroacetimidate methods give the higher yields. (127)



X	Mediator	Temp	
$\beta$ -SPh	BSP, Tf <sub>2</sub> O, TTBP*	-60°	(78%) $\alpha:\beta = 6.2:1$
$\beta$ -S(O)Ph	Tf <sub>2</sub> O, TTBP*	-60°	(63%) $\alpha$ only
$\alpha,\beta$ -OH	Ph <sub>2</sub> SO, Tf <sub>2</sub> O, TTBP*	-40°	(59%) $\alpha$ only
$\alpha$ -OC(=NH)CCl <sub>3</sub>	TMSOTf	-30°	(82%) $\alpha:\beta = 3.5:1$

The sulfoxide, thioglycoside, and dehydrative methods are typically conducted in the presence of base, which obviously renders them suitable for acid sensitive substrates. This is in contrast to the imidate method which necessarily functions under Lewis acidic conditions and which is reported (52) to fail in the presence of simple basic groups such as pyridyl (Eq. 57). In the example depicted in Eq. 57, the majority of the trichloroacetimidate is recovered unchanged.



In the case of the 2,3-anhydro-lyxofuranosyl donors (Eq. 20), it was found that activation of the sulfoxide with triflic anhydride provides better yields overall than activation of the corresponding thioglycosides with *N*-iodosuccinimide/silver triflate. (72) This situation arises because a hindered base may be included in glycosylations conducted by the sulfoxide method to buffer the triflic acid generated, whereas the *N*-iodosuccinimide/silver triflate method fails in the presence of base and, thus, is not applicable to acid-sensitive substrates. With the thioglycoside 2,3-anhydrolyxofuranosyl donors an acid-catalyzed rearrangement leading, overall, to the formation of 2-deoxy-2-(*p*-thiitoluyl)- $\beta$ -D-xylofuranosides is found to compete with the desired formation of the 2,3-anhydroglycosides when the *N*-iodosuccinimide/silver triflate couple is the promoter. (72) In addition, better yields and stereoselectivities are observed by the sulfoxide/triflic anhydride method leading to the conclusion that the method is superior to *N*-iodosuccinimide/silver triflate promoted couplings with analogous thioglycosides. Although only a strictly limited number of examples were conducted, the activation of the 2,3-anhydrothioglycosides in the presence of a hindered base by the sulfinamide/triflic anhydride method gives identical stereoselectivities to the sulfoxide method, albeit with slightly reduced yields. (72)

Rather than attempting any further comparisons here, which would be

necessarily speculative in view of the sparse data available, it is perhaps best to simply point out again the considerable attributes of the methods presented in this chapter. The main strengths of the sulfoxide and thioglycoside methods, proceeding mainly through the glycosyl triflate intermediates, are as follows: first, the ability to glycosylate even the most hindered of alcohols, without the need for precious- or heavymetal promoters, in a matter of minutes at low temperatures; second, the capacity to form each of the four common classes of glycosidic bond (1,2-cis-equatorial; 1,2-cis-axial; 1,2-trans-equatorial, and 1,2-trans-axial); and, third, the use of a very limited set of conditions to form a wide range of different glycosidic bonds. (99) The sulfoxide method is often disparaged because of the need to prepare a thioglycoside and then convert it into the sulfoxide, thereby adding an extra step to any sequence. In reality this is a very minor inconvenience when compared to the gain in reactivity over most thioglycoside methods in use (164-166) prior to the advent of the thioglycoside/sulfinatate chemistry. When compared to the extremely popular and potent imidate method, (160-163) the need to oxidize the thioglycoside to the sulfoxide is even less of an inconvenience; after all the imidate has to be prepared by a two-step sequence involving release of the anomeric hydroxyl group from a protected form and subsequent conversion into the somewhat unstable trichloroacetimidate before coupling can be carried out.

The dehydrative method employing hemiacetals, a diaryl sulfoxide, and triflic anhydride is a powerful and direct approach to glycosidic bond formation. Of all the glycosylations carried out in 1994, (158) only a handful used direct dehydrative methods and it is evident that the chemistry described here is superior in terms of convenience and reactivity to those earlier methods. (22) A more appropriate comparison is perhaps with the imidate method (160-163) as this too requires liberation of the anomeric hydroxyl group prior to coupling. The obvious practical difference is that the dehydrative method requires no further handling of the hemiacetal, which may be used directly for the coupling reaction, whereas the imidate method necessitates prior derivatization of the anomeric hydroxyl group. The clear advantage of the trichloroacetimidate method is that, once the derivative is formed, the coupling is usually carried out with only a catalytic quantity of silyl triflate as promoter.

The glycal method is very different from the other reactions surveyed in this chapter because the actual glycosylations, which occur only after the intermediate 1,2-anhydro donor has been formed, are much slower and are conducted at higher temperatures. The most germane comparison here is with the other common variant on the glycal method, namely that forming the intermediate 1,2-anhydro donor by simple action of dimethyldioxirane. (56, 174-177) The sulfoxide/triflic anhydride approach to oxidative glycosylation has the obvious advantage over the dimethyldioxirane method of using a combination of readily available shelf-stable reagents to bring about the key

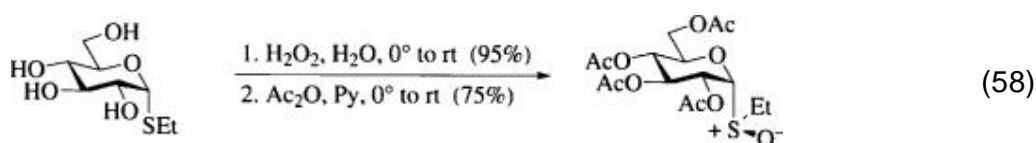
transformation. On the other hand, activation of the glycal with dimethyl dioxirane produces only acetone as byproduct, thereby simplifying work-up considerably. The sulfoxide/triflic anhydride method of activating the glycal has the major advantage of enabling, through judicious choice of the sulfoxide, the formation of manno-1,2-anhydro sugars and so the direct formation of  $\alpha$ -mannosides. In the conversion of glycals into 2-deoxy-2-acetamido glycosides the sulfoxide/triflic anhydride variant, operating in the presence of *N*-trimethylsilylacetamide, provides the 2-acetamido glycoside directly, (57) which distinguishes it from all other glycal based routes to this important class of linkage. (56, 174-177)

Direct comparisons between the four methods described in this chapter are as rare as those with other methods. Among the four systems the oxidative glycosylation of glycals stands out because of the considerably lower reactivity of the intermediate 1,2-anhydropyranose and the consequent need for longer reaction times and, typically, for Lewis acid activation. The sulfoxide, thioglycoside, and dehydrative methods, however, function under very similar conditions and share a relative ease of operation. One obvious advantage of the thioglycoside method over the sulfoxide method is the absence of the competing glycosylation pathway going via glycosyl sulfenates (Eq. 8). On the other hand, the thioglycoside method, because of solubility concerns with the reagents, is typically conducted at  $-60^\circ$  rather than  $-78^\circ$ . This difference in temperature leads to a minor erosion of selectivity as is evident in the one published direct comparison of the two methods. (182)

## 7. Experimental Conditions

### 7.1. Thioglycosides and Glycosyl Sulfoxides

While the preparation of thioglycosides is long established and well documented, (164-166) the formation of glycosyl sulfoxides requires comment. Aqueous hydrogen peroxide has been used to oxidize *S*-ethyl  $\alpha$ -D-thioglucofuranoside to the sulfoxide in excellent yield. (183) The hydroxy groups of the product could then be acetylated to give the tetraacetate. (183) It was reported that the sulfoxide is formed as a single diastereomer and, in the light of subsequent work, (96, 98, 101) it can be confidently assigned as the  $S_R$  diastereomer (Eq. 58).



Most of the common reagents for the oxidation of sulfides to sulfoxides have been applied to peracetylated *S*-aryl thioglycosides including perbenzoic acid, (184) sodium metaperiodate, (96) Oxone<sup>®</sup>, (59, 96) *tert*-butyl hypochlorite, (98) the urea/hydrogen peroxide complex, (185) and hydrogen peroxide in acetic acid. (186) By far the most common reagent for the oxidation of protected thioglycosides to the corresponding sulfoxides, however, has been *m*-CPBA. (9, 27, 99) The need to carefully monitor *m*-CPBA reactions and to maintain low temperatures in order to prevent over-oxidation to the unproductive sulfone, however, drives the continued development of more practical alternative methods for this transformation. Magnesium monoperoxyphthalate (MMPP) has been successfully used on numerous occasions, with results comparable to well-controlled *m*-CPBA oxidations. These oxidations are conveniently conducted in aqueous THF at room temperature. (84, 95) The use of 30% hydrogen peroxide in dichloromethane and acetic anhydride is reported to provide glycosyl sulfoxides in excellent yield at room temperature, with little over-oxidation to the sulfone, provided that the reaction is conducted in the presence of silica gel. (185) Indeed, this procedure has been used to oxidize *S*-phenyl 2,3,4,6-tetra-*O*-benzyl-  $\beta$ -D-thioglucofuranoside to the corresponding sulfoxides in 98% yield on a scale of 15 kg. (115) It has been reported that oxidation with H<sub>2</sub>O<sub>2</sub>/ Ac<sub>2</sub>O / SiO<sub>2</sub> is more rapid when conducted in mixtures of dichloromethane and perfluorinated hydrocarbons as opposed to dichloromethane alone. (187) It was also noted that this combination brings about oxidation of armed thioglycosides more rapidly than disarmed ones. (187) The use of silica gel to support Oxone<sup>®</sup> and *tert*-butylhydroperoxide is

also reported to suppress overoxidation to sulfones in the oxidation of thioglycosides to glycosyl sulfoxides. (188)

1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor™) is reported to bring about the efficient oxidation of aryl thioglycosides to sulfoxides in very high yield in aqueous acetonitrile, (189) as is the simple use of 30% hydrogen peroxide in hexafluoro-2-propanol. (190)

## 7.2. 1-Hydroxy Sugars (Hemiacetals)

The dehydrative method shares with the trichloroacetimidate method the need for the preparation of otherwise fully protected 1-hydroxy sugars. In view of the very widespread use of the trichloroacetimidate method numerous protocols are available for revealing the anomeric hydroxy group in the presence of a broad range of protecting groups around the periphery of the sugar ring. Accordingly, the reader is referred to the extensive literature on trichloroacetimidate couplings. (160-163, 191)

## 7.3. Glycals

Methods for the synthesis of glycals, the substrates for the oxidative coupling sequence, are very well established. Glycals have long been in use as precursors to 2-deoxy sugars (192, 193) and, more recently, have been vigorously exploited in the so-called “glycal assembly” method both in solution and on polymeric supports. As such the preparations of numerous diversely protected glycals are described in the original literature to which the reader is referred. (56, 175-177) It should also be noted that a considerable number of glycals are available commercially from the Aldrich Chemical Company.

## 7.4. Solvent

The most common solvent for the sulfoxide and thioglycoside methods is dichloromethane. Toluene is also an option as is ether but it must be recognized that these solvents, especially ether, have an effect on the covalent triflate/glycosyl cation and triflate anion equilibrium and so can change the stereoselectivity of the coupling, particularly in the case of  $\beta$ -mannosylation. Propionitrile is a participating solvent that is a mobile liquid at  $-78^\circ$ , unlike acetonitrile, and it has found use in the preparation of  $\beta$ -glucosides with donors incapable of neighboring group participation. Dichloromethane and mixtures of dichloromethane with toluene have been the most commonly employed solvents for the dehydrative method. The various oxidative glycosylations favor dichloromethane or mixtures of dichloromethane with chloroform.

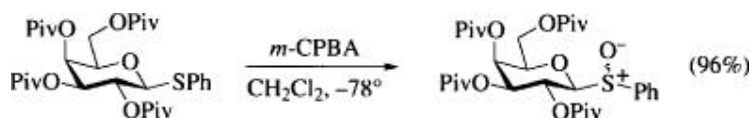
## 7.5. Bases and Other Scavengers

The sulfoxide, thioglycoside, and dehydrative methods are typically conducted in the presence of a non-nucleophilic base to buffer the triflic acid generated in the course of the reaction. The 2,6-di-*tert*-butylated pyridines (4-H, DTBP), (4-Me, DTBMP), and (4-*t*-Bu, TTBP) are all suitable and have been employed

for this purpose. The more crystalline, less hygroscopic 2,4,6-tri-*tert*-butylpyrimidine (TTBP\*) is a convenient alternative to these low melting, hygroscopic bases. (26) The dehydrative method was originally conducted with 2-chloropyridine as base but, in view of its ability to participate in the formation of glycosyl pyridinium intermediates, the hindered pyridines and TTBP\* are probably preferable, and have already been shown to function well in applications of this method. (25, 52) Although bases are most commonly employed in all three aforementioned methods, they can sometimes result in the formation and isolation of orthoesters rather than glycosides. (18, 59-62) Frequently, this problem can be circumvented by simple omission of the base provided no overly acid sensitive protecting groups are present. (18, 64, 66, 106) Other scavengers that have been employed in the sulfoxide method to trap sulfenic acids and esters and thereby protect electron-rich functional groups, including other thioglycosides, are methyl propiolate (Eq. 22), (10, 11) allyl-1,2-dimethoxybenzene, (70) trimethyl phosphite, (10) and triethyl phosphite. (12, 19) In particular, it should be noted that the use of trimethyl and triethyl phosphite as scavengers, in both the sulfoxide and the thioglycoside methods, permits the use of acceptors bearing the thioglycoside function as depicted in Eq. 44. (12, 19) Bases ranging from *N,N*-diethylaniline to triethylamine and diisopropylethylamine are used in conjunction with the oxidative glycosylation sequences and Table 4 should be consulted to determine which one is appropriate for a particular sequence. The addition of powdered 3, 4, or 5 Å molecular sieves to glycosylation reactions to minimize hydrolysis by adventitious moisture is a very common practice in carbohydrate chemistry. In many of the examples in the Tables such a procedure has been followed but in equally many it has not. There is at present no evidence for or against the intervention of molecular sieves in these reactions other than by sequestering water.

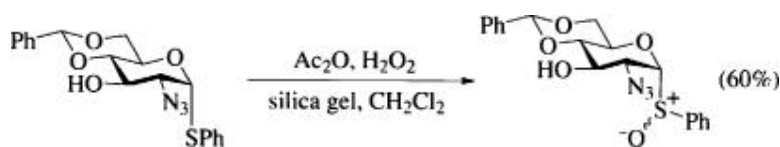


## 8. Experimental Procedures



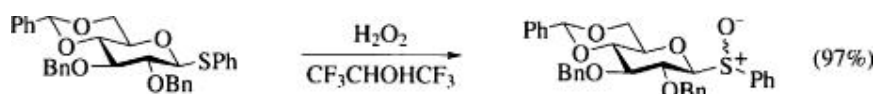
### 8.1.1.1. Phenyl 2,3,4,6-Tetra-O-pivaloyl-1-thio- $\beta$ -D-galactopyranoside S-Oxide [Oxidation of a Thioglycoside with *m*-CPBA] (99)

To a solution of phenyl 2,3,4,6-tetra-O-pivaloyl-1-thio- $\beta$ -D-galactopyranoside (7.50 g, 12.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) at  $-78^\circ$  was added *m*-CPBA (3.33 g, 12.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL). After 15 minutes of stirring at  $-78^\circ$ , the mixture was poured into saturated aqueous  $\text{NaHCO}_3$  (500 mL). The organic layer was washed with saturated aqueous  $\text{NaHCO}_3$  ( $2 \times 500$  mL), dried over  $\text{Na}_2\text{SO}_4$ , concentrated, and the residue was purified by flash chromatography (20% EtOAc in petroleum ether) to afford the title sulfoxide (7.4 g, 96%, diastereomeric ratio: 2.1:1 favoring the more polar product) as a white solid: HRMS-FAB ( $m/z$ ):  $[\text{M}]^+$  calcd for  $\text{C}_{32}\text{H}_{48}\text{O}_{10}\text{S}$ , 624.2968; found, 624.2968. Less polar isomer ( $R_f = 0.41$ , 20% EtOAc in petroleum ether):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.7–7.5 (m, 5H), 5.56 (t,  $J = 9.9$  Hz, 1H), 5.38 ( $J = 3.3$  Hz, 1H), 5.18 (dd,  $J = 3.1, 10.1$  Hz, 1H), 4.46 (d,  $J = 9.9$  Hz, 1H), 4.44–3.91 (m, 3H), 1.24, 1.15, 1.10 (s,  $4 \times 9\text{H}$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  177.7, 177.3, 176.7, 176.0, 138.7, 131.5, 128.8, 125.8, 89.4, 75.5, 72.1, 66.4, 64.3, 61.0, 38.9, 38.8, 38.7, 38.6, 27.0, 26.9. More polar isomer ( $R_f = 0.25$ , 20% EtOAc in petroleum ether):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.8–7.5 (m, 5H), 5.31 (d,  $J = 2.6$  Hz, 1H), 5.16 (dd,  $J = 3.0, 9.6$  Hz, 1H), 5.09 (dd,  $J = 9.6, 9.9$  Hz, 1H), 4.68 (d,  $J = 9.6$  Hz, 1H), 4.13–4.03 (m, 2H), 3.78–3.68 (m, 1H), 1.25, 1.16, 1.09, 0.94 (s,  $4 \times 9\text{H}$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  177.6, 177.0, 176.9, 137.0, 132.0, 128.6, 127.1, 92.2, 75.0, 71.7, 66.0, 64.8, 60.2, 38.9, 38.7, 38.6, 27.0, 26.8.



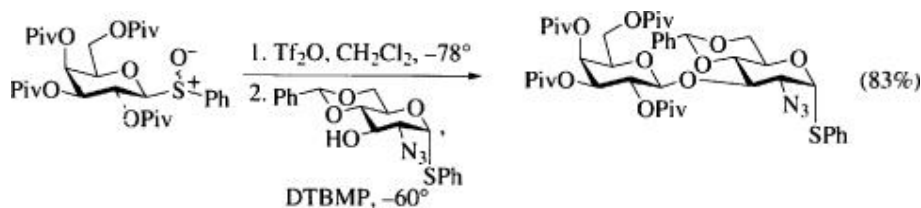
### 8.1.1.2. Phenyl 2-Azido-2-deoxy-4,6-O-benzylidene-1-thio- $\alpha$ -D-glucopyranoside S-Oxide [Oxidation of a Thioglycoside with Acetic Anhydride/Hydrogen Peroxide and Silica Gel] (185)

To a stirred mixture of phenyl 2-azido-4,6-O-benzylidene-2-deoxy-1-thio-  $\alpha$ -D-glucopyranoside (**99**) (1 mmol), Ac<sub>2</sub>O (1.1 mmol), and silica gel (200 mg, 230–400 mesh) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added aqueous 30% H<sub>2</sub>O<sub>2</sub> solution (1.2 mmol). After being stirred at room temperature between 2 and 24 hours the reaction mixture (monitored by TLC) was filtered through a sintered glass funnel and the filtrate washed with saturated aqueous NaHSO<sub>3</sub> (50 mL), NaHCO<sub>3</sub> (50 mL), and brine (50 mL). The organic layer was separated, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and the residue was purified by chromatography on silica gel using gradient elution (25%–40% EtOAc in hexane) to give the title sulfoxide (60%), mp 151–153°; IR (KBr) 3364, 2214 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.76–7.35 (m, 10H), 5.51 (s, 1H), 4.69 (d, *J* = 5.7 Hz, 1H), 4.60 (td, *J* = 3.3, 9.0 Hz, 1H), 4.16–4.00 (m, 2H), 3.98–3.88 (m, 1H), 3.64–3.50 (m, 2H), 3.43 (br s, 1H). Anal. Calcd for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>O<sub>5</sub>S : C, 56.84; H, 4.77; N, 10.47; S, 7.97. Found: C, 56.54, H, 4.89; N, 10.31; S, 7.87.



8.1.1.3. Phenyl 2,3-Di-O-benzyl-4,6-O-benzylidene-1-thio-  $\beta$ -D-glucopyranoside S-Oxide [Oxidation of a Thioglycoside with Hydrogen Peroxide in Hexafluoro-2-propanol] (**190**)

Aqueous 30% H<sub>2</sub>O<sub>2</sub> (0.1 mL, 1 mmol) was added to a stirred solution of phenyl 2,3-di-O-benzyl-4,6-O-benzylidene-1-thio-  $\beta$ -D-glucopyranoside (0.27 g, 0.50 mmol) in hexafluoro-2-propanol (2.5 mL) at 25°. After the complete disappearance (TLC) of the sulfide (3 hours), the excess H<sub>2</sub>O<sub>2</sub> was quenched with saturated Na<sub>2</sub>SO<sub>3</sub> solution (2.0 mL) and the fluoruous phase containing the sulfoxide was separated. After distillation of hexafluoro-2-propanol, the title sulfoxide was obtained as a white solid (0.27 g, 97%), mp 144°; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.0–7.7 (m, 20H), 5.53 (s, 1H), 4.6 (d, *J* = 9.1 Hz, 0.5H), 4.42 (m, 0.5H), 4.16 (dd, *J* = 8.5, 9.8 Hz, 0.5H), 4.02 (d, *J* = 9.8 Hz, 0.5H), 4.0 (dd, *J* = 5, 10.5 Hz, 0.5H), 3.92 (m, 1H), 3.85 (dd, *J* = 7.7, 9.1 Hz, 0.5H), 3.79 (t, *J* = 9.3 Hz, 0.5H), 3.75 (t, *J* = 10.5 Hz, 0.5H), 3.70 (m, 0.5H), 3.58 (m, 1H), 3.30 (td, *J* = 5, 9.7 Hz, 0.5H); <sup>13</sup>C NMR  $\delta$  122–132, 101.5, 94/96, 83, 81, 75/76.5, 70.2/71, 68. Anal. Calcd for C<sub>33</sub>H<sub>32</sub>O<sub>6</sub>S : C, 71.19; H, 5.81; S, 5.76. Found: C, 71.16; H, 5.92; S, 5.66.



8.1.1.4. Phenyl 3-O-(2,3,4,6-Tetra-O-pivaloyl- $\beta$ -D-galactopyranosyl)-2-azido-4,6-O-benzylidene-2-deoxy-1-thio- $\alpha$ -D-glucopyranoside [Typical Glycosylation with Preactivation] (99)

To a solution of S-phenyl 2,3,4,6-tetra-O-pivaloyl-1-thio- $\beta$ -D-galactopyranoside S-oxide (99) (109 mg, 0.175 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) at  $-78^\circ$  was added  $\text{Tf}_2\text{O}$  (15  $\mu\text{L}$ , 0.089 mmol), and then the mixture was warmed to  $-60^\circ$ . After 15 minutes of stirring the mixture at  $-60^\circ$ , phenyl 2-azido-4,6-O-benzylidene-2-deoxy-1-thio- $\alpha$ -D-glucopyranoside (99) (37 mg, 0.096 mmol) and DTBMP (110 mg, 0.526 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) were added dropwise via syringe. After 10 minutes of stirring at  $-60^\circ$ , the mixture was warmed to  $-30^\circ$  over 30 minutes, quenched by saturated aqueous  $\text{NaHCO}_3$  (5 mL), and washed with saturated aqueous  $\text{NaHCO}_3$  ( $2 \times 100$  mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , concentrated, and the residue was purified by flash chromatography (13% EtOAc in petroleum ether) to afford the disaccharide (70 mg, 83%) as a white solid,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.5–7.2 (m, 10H), 5.60 (d,  $J = 4.4$  Hz, 1H), 5.55 (s, 1H), 5.34 (d,  $J = 2.6$  Hz, 1H), 5.27 (dd,  $J = 8.1, 10.3$  Hz, 1H), 5.08 (dd,  $J = 3.5, 10.5$  Hz, 1H), 4.87 (d,  $J = 8.1$  Hz, 1H), 4.40 (td,  $J = 4.8, 9.9$  Hz, 1H), 4.19 (dd,  $J = 5.0, 10.5$  Hz, 1H), 4.05–4.04 (m, 2H), 4.00 (dd,  $J = 8.4, 10.6$  Hz, 1H), 3.94 (dd,  $J = 6.2, 11.0$  Hz, 1H), 3.79–3.75 (m, 2H), 3.72 (dd,  $J = 7.0, 8.1$  Hz, 1H), 1.23, 1.22, 1.14, 1.11 (s,  $4 \times 9\text{H}$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  177.6, 177.3, 176.8, 176.6, 136.8, 132.7, 132.5, 129.3, 129.2, 128.4, 128.1, 126.0, 101.7, 100.5, 87.3, 80.2, 77.1, 71.1, 70.9, 69.3, 68.5, 66.3, 63.6, 63.5, 60.6, 39.0, 38.9, 38.7, 38.6, 27.2, 27.1; HRMS-FAB ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{45}\text{H}_{60}\text{O}_{13}\text{N}_3\text{S}$ , 882.3847; found, 882.3861.

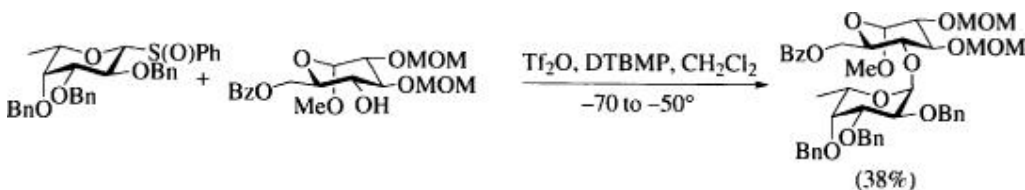


8.1.1.5. 2-[(*tert*-Butyldiphenylsiloxy)methyl]-5-[(4-*O*-acetyl-3-*O*-methyl-2-*O*-pivaloyl- $\alpha$ -*D*-rhamnopyranosyl)oxy]-3,4-dimethoxy-6-iodotoluene [Glycosylation of an *O*-Tributylstannyl Phenol] (117)

To a suspension of

4-[(*tert*-butyldiphenylsilyloxy)methyl]-2-iodo-5,6-dimethoxy-3-methylphenol (319 mg, 0.567 mmol, 1.0 equiv) and crushed 4 Å molecular sieves in benzene (15 mL) was added (Bu<sub>3</sub>Sn)<sub>2</sub>O (177  $\mu$ L, 0.34 mmol, 0.6 equiv). The reaction mixture was heated to reflux for 4 hours, and the sieves were removed by filtration through a plug of Celite<sup>®</sup>. After removing the water from the reaction mixture by azeotroping with toluene (2  $\times$  5 mL), the crude product was kept under Ar, and used immediately for the glycosidation.

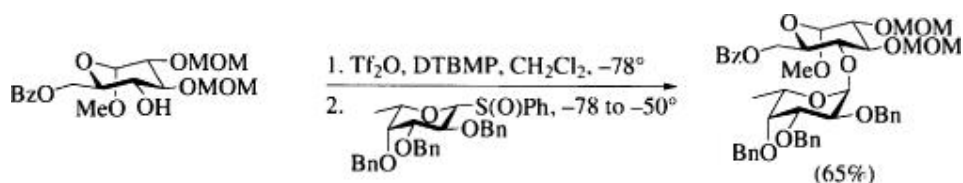
To a solution of *S*-phenyl 4-*O*-acetyl-3-*O*-methyl-2-*O*-pivaloyl-1-thio- $\alpha$ -*L*-rhamnopyranoside *S*-oxide (117) (476 mg, 1.13 mmol) and DTBMP (255 mg, 1.13 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) at -60° was added Tf<sub>2</sub>O (210  $\mu$ L, 1.24 mmol). The solution was stirred at -60° for 30 minutes before tributyl(4-[(*tert*-butyldiphenyl-siloxy)methyl]-2-iodo-5,6-dimethoxy-3-methylphenoxy)stannane (from preparation described above) in CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL) was added dropwise over a period of 5 minutes. After 30 minutes, the reaction flask was removed from the cold bath, stirred at 25° for 3 minutes, and the reaction quenched by pouring over saturated aqueous NaHCO<sub>3</sub> (50 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated, and the residue was purified by flash chromatography (20% Et<sub>2</sub>O in petroleum ether) to give the glycoside (480 mg, 99%) as a colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  5.78 (dd, *J* = 2, 3 Hz, 1H), 5.47 (d, *J* = 1.7 Hz, 1H), 5.09 (d, *J* = 9.9 Hz, 1H), 4.75 (s, 2H), 4.38 (dq, *J* = 6, 10 Hz, 1H), 4.02 (dd, *J* = 3, 9.6 Hz, 1H), 3.75 (s, 3H), 3.63 (s, 3H), 3.4 (s, 3H), 2.49 (s, 3H), 2.11 (s, 3H), 1.24 (s, 9H), 1.19 (d, *J* = 6.2 Hz, 3H), 1.03 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  177.6, 170.2, 153.0, 149.7, 142.9, 138.0, 135.8, 133.5, 129.6, 129.1, 127.6, 101.1, 93.8, 77.2, 72.3, 69.0, 67.7, 61.3, 60.7, 58.6, 57.5, 39.1, 27.2, 26.9, 25.5, 21.1, 19.3, 17.6.



8.1.1.6. Methyl 4-*O*-(2,3,4-*Tri*-*O*-benzyl)- $\alpha$ -*L*-fucopyranosyl)-6-*O*-benzoyl-2,3-di-*O*-(methoxymethyl)- $\alpha$ -*D*-glucopyranoside [Typical Glycosylation with Premixing] (51)

A mixture of *S*-phenyl 2,3,4-tri-*O*-benzyl-1-thio- $\beta$ -*L*-fucopyranoside *S*-oxide (99) (80 mg, 0.15 mmol), methyl 6-*O*-benzoyl-2,3-di-*O*-(methoxymethyl)- $\alpha$

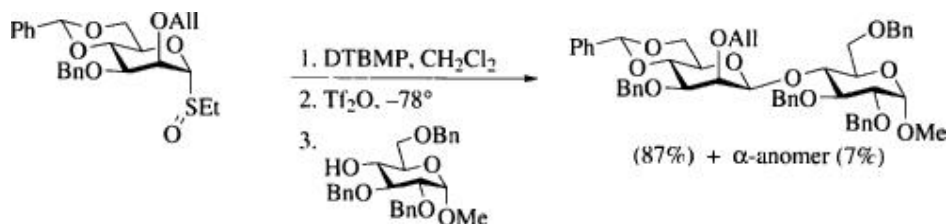
-D-glucopyranoside (**51**) (25 mg, 0.065 mmol), and DTBMP (223 mg, 1.09 mmol) was azeotroped three times with toluene (10 mL). To the residue dissolved in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) were added 4 Å molecular sieves (0.5 g), and the resulting suspension was stirred at room temperature for 1 hour. The suspension was cooled to -78°, and a solution of Tf<sub>2</sub>O (45 µL, 0.27 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (350 µL) was added over 1–2 minutes. The reaction mixture was warmed to -50°, and after 15 minutes at -50°, was filtered into saturated aqueous NaHCO<sub>3</sub> (30 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The extracts were purified by flash chromatography (33% EtOAc in petroleum ether) to afford the disaccharide (20 mg, 38%), <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.03 (d, *J* = 6.9 Hz, 2H), 7.15–7.65 (m, 18H), 5.03 (d, *J* = 3.6 Hz, 1H), 4.95 (d, *J* = 11.5 Hz, 1H), 4.6–4.9 (m, 11H), 4.52 (dd, *J* = 4.3, 12.2 Hz, 1H), 4.25 (q, *J* = 6.3 Hz, 1H), 4.07 (dd, *J* = 3.6, 10.2 Hz, 1H), 3.8–4.0 (m, 3H), 3.74 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.68 (br s, 1H), 3.53 (dd, *J* = 3.6, 9.3 Hz, 1H), 3.39 (s, 3H), 3.38 (s, 3H), 3.36 (s, 3H), 1.11 (d, *J* = 6.3 Hz, 3H); <sup>13</sup>C NMR (CD<sub>3</sub>COCD<sub>3</sub>) δ 166.6, 140.4, 140.2, 139.8, 130.3, 129.5, 129.2, 129.1, 129.0, 129.0, 128.7, 128.4, 128.3, 128.2, 128.2, 100.0, 99.9, 99.3, 98.4, 80.5, 79.3, 79.0, 77.2, 77.1, 75.7, 74.5, 73.0, 69.9, 68.1, 64.7, 56.6, 55.5, 55.3, 17.1; HRMS-FAB (*m/z*): [M + H]<sup>+</sup> calcd for C<sub>45</sub>H<sub>53</sub>O<sub>13</sub>, 801.3486; found, 801.3499.



8.1.1.7. Methyl 4-O-(2,3,4-Tri-O-benzyl-*α*-L-fucopyranosyl)-6-O-benzoyl-2,3-di-O-(methoxymethyl)-*α*-D-glucopyranoside [Glycosylation with Inverse Addition of the Sulfoxide to the Acceptor and Tf<sub>2</sub>O] (**51**)

A mixture of the acceptor, methyl 6-O-benzoyl-2,3-di-O-(methoxymethyl)-*α*-D-glucopyranoside, (**51**) (25 mg, 0.065 mmol) and DTBMP (220 mg, 1.07 mmol) was azeotroped three times with toluene (10 mL). To the residue in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) were added 4 Å molecular sieves (500 mg), and the resulting suspension was stirred at room temperature for 1 hour. The suspension was cooled to -78°, and a solution of Tf<sub>2</sub>O (45 µL, 0.27 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (350 µL) was added over 1–2 minutes. A solution of S-phenyl 2,3,4-tri-O-benzyl-1-thio-β-L-fucopyranoside S-oxide (**99**) (80 mg, 0.15 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added via syringe over 10–15 minutes. The reaction mixture was warmed to -50°, and after 15 minutes at -50°, the reaction mixture was filtered into saturated aqueous NaHCO<sub>3</sub> (30 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL).

The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The extracts were purified by flash chromatography (33% EtOAc in petroleum ether) affording the disaccharide (34 mg, 65%) with data as given in the immediately preceding experimental description.



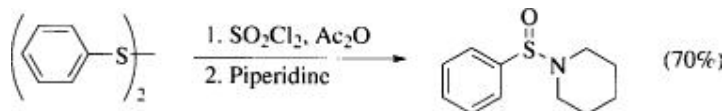
#### 8.1.1.8. Methyl

2,3,6-Tri-O-benzyl-4-O-(2-O-allyl-3-O-benzyl-4,6-O-benzylidene-β-D-mannopyranosyl)-α-D-glucopyranoside and the α-Anomer [Typical β-Mannosylation] (59)

To a stirred solution of S-ethyl 2-O-allyl-3-O-benzyl-4,6-O-benzylidene-1-thio-α-D-mannopyranoside S-oxide (59) (428 mg, 0.93 mmol) and DTBMP (377 mg, 1.83 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) at -78° under an Ar atmosphere was added Tf<sub>2</sub>O (173 μL, 1.02 mmol). After 5 minutes, a solution of the acceptor, methyl 2,3,6-tri-O-benzyl-α-D-glucopyranoside, (194) (818 mg, 1.76 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added dropwise. The reaction mixture was stirred at -78° for 1 hour then warmed gradually to 0°, quenched with saturated aqueous NaHSO<sub>3</sub>, the organic phase was washed with brine, and dried (Na<sub>2</sub>SO<sub>4</sub>). Concentration and chromatography on silica gel (20% EtOAc in hexane) gave the β-disaccharide (731 mg, 87%) and the α-anomer (60 mg, 7%). β-Anomer: [α]<sub>D</sub><sup>20</sup> - 12.1° (c 1.5, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.50–7.20 (m, 25H); 5.90–6.04 (m, 1H), 5.52 (s, 1H), 5.28 (d, J = 18.4 Hz, 1H), 5.13 (d, J = 11.4 Hz, 1H), 5.11 (d, J = 10.5 Hz, 2H), 4.86–4.76 (m, 3H), 4.70–4.60 (m, 4H), 4.35 (d, J = 11.8 Hz, 2H), 4.29 (m, 2H), 4.10–4.00 (m, 2H), 3.96–3.88 (m, 2H), 3.80–3.51 (m, 5H), 3.40 (s, 3H), 3.32 (dd, J = 3.5, 9.7 Hz, 1H), 3.05 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 139.3, 138.0, 137.5, 136.5, 135.4, 128.8, 128.5, 128.3, 128.0, 127.7, 127.5, 127.3, 125.9, 116.8, 101.2 (2 C), 98.3, 80.1, 78.6, 77.8, 77.4, 77.0, 75.2, 74.4, 73.5 (2 C), 72.4, 69.5, 68.5, 68.2, 67.1, 55.3. Anal. Calcd for C<sub>51</sub>H<sub>56</sub>O<sub>11</sub>·1H<sub>2</sub>O : C, 70.97; H, 6.77. Found: C, 70.93; H, 6.64.

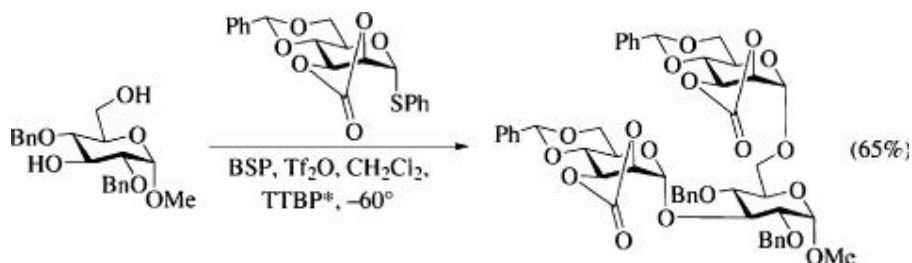
α-Anomer: [α]<sub>D</sub><sup>20</sup> + 21° (c 3, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.55–7.20 (m, 25H), 5.66 (m, 1H), 5.59 (s, 1H), 5.11 (d, J = 11.7 Hz, 1H), 5.06 (d, J = 17.3 Hz, 1H), 5.00 (d, J = 10.3 Hz, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.75–4.50 (m, 7H), 4.18 (m, 1H), 4.10 (m, 1H), 4.00–3.75 (m, 7H), 3.39 (s, 3H), 3.75–3.65 (m, 5H), 3.55 (dd, J = 3.5, 9.5 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 138.5, 137.9, 137.7, 134.7, 128.7, 128.4, 128.3, 128.2, 128.0, 127.9, 127.6, 127.4, 126.7, 126.0, 116.8,

101.6, 101.3, 97.7, 81.4, 79.9, 78.9, 77.4, 77.0, 75.8, 73.5, 73.1, 72.9, 72.7, 69.5, 68.8, 68.6, 65.0, 55.3.



#### 8.1.1.9. Preparation of 1-Benzenesulfinylpiperidine (18)

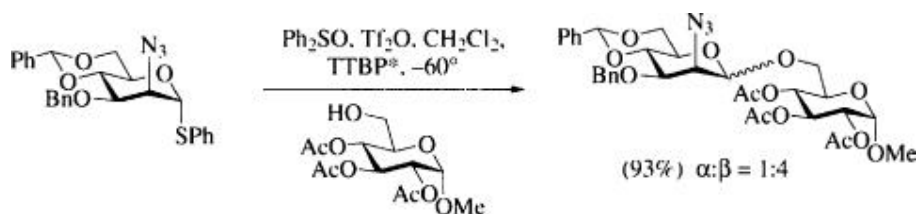
Sulfuryl chloride (58.9 mL, 0.73 mol) was slowly added to a mixture of diphenyl disulfide (40 g, 0.18 mol) and acetic anhydride (51.8 mL, 0.55 mol) cooled to 0°. The reaction mixture was stirred for 2 hours, with monitoring of aliquots by <sup>1</sup>H-NMR to ensure conversion of the disulfide, and the resulting solution was concentrated under reduced pressure. The resulting PhSOCl was used without further purification. A solution of PhSOCl (58.0 g, 0.365 mol) in diethyl ether (200 mL) was slowly added at 5° to a cooled solution of piperidine (72 mL, 0.73 mol) in diethyl ether (200 mL). The reaction mixture was stirred at room temperature for 1 hour, filtered and then concentrated under reduced pressure. The solid residue was triturated with hexanes to give the title product as a white crystalline solid (53.4 g, 70%), mp 84–85°, lit. (195) mp 83–84°; <sup>1</sup>H NMR δ 7.59–7.56 (m, 2H), 7.42–7.37 (m, 3H), 2.87–2.83 and 3.04–2.89 (each m, 2H), 1.53–1.41 (m, 6H); <sup>13</sup>C NMR δ 143.3, 130.6, 128.7, 126.1, 46.9, 26.1, 23.8; EIMS (*m/z*): [M + H]<sup>+</sup> 210.



#### 8.1.1.10. Methyl 2,4-Di-O-benzyl-3-O-(2,3-O-carbonyl-4,6-O-benzylidene-α-D-mannopyranosyl)-6-O-(2,3-O-carbonyl-4,6-O-benzylidene-α-D-mannopyranosyl)-α-D-mannoside [Double Glycosylation by the Thioglycoside/Sulfinate Method] (18)

To a stirred solution containing S-phenyl 4,6-O-benzylidene-2,3-O-carbonyl-1-thio-α-D-mannopyranoside (140) (0.14 g, 0.36 mmol), BSP (0.080 g, 0.38 mmol), TTBP\* (0.16 g, 0.66 mmol), and activated 3 Å powdered sieves in CH<sub>2</sub>Cl<sub>2</sub> (5 mL), at -60° under an argon atmosphere, was added Tf<sub>2</sub>O (0.064 mL, 0.39 mmol). After 5 minutes, a

solution of methyl 2,4-di-O-benzyl-  $\alpha$ -D-mannopyranoside (**196**) (0.062 g, 0.17 mmol) in dichloromethane (2 mL) was added. The reaction mixture was warmed to room temperature, filtered, washed with saturated aqueous  $\text{NaHCO}_3$  followed by brine, dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (50% EtOAc in hexanes) to give the title product as a clear viscous oil (0.10 g, 65%),  $[\alpha]_D^{20} + 11.7^\circ$  (c 0.8);  $^1\text{H NMR}$  ( $\text{C}_6\text{D}_6$ )  $\delta$  7.63–7.24 (m, 20H), 5.49 and 5.43 (each s, 1H), 5.15 and 5.11 (each s, 1H), 4.70 (d,  $J = 11$  Hz, 1H), 4.66 (d,  $J = 1.5$  Hz, 1H), 4.63 (d,  $J = 11$  Hz, 1H), 4.50 (d,  $J = 11.5$  Hz, 1H), 4.43 and 4.39 (each  $J = 7.5$  Hz, 1H), 4.33 (d,  $J = 11.5$  Hz, 1H), 4.28–4.25 (m, 2H), 4.20 (dd,  $J = 5, 10$  Hz, 1H), 4.17 (q,  $J = 10$  Hz, 1H), 4.10 (dd,  $J = 5, 10$  Hz, 1H), 4.06 (d,  $J = 7$  Hz, 1H), 3.87 (dt,  $J = 5, 10$  Hz, 1H), 3.73–3.78 (m, 2H), 3.65–3.68 (m, 2H), 3.58–3.62 (m, 2H), 3.52 (dd,  $J = 8, 10$  Hz, 1H), 3.37 and 3.44 (each t,  $J = 10.5$  Hz, 1H), 3.13 (s, 3H);  $^{13}\text{C NMR}$   $\delta$  137.8, 137.7, 136.9, 136.8, 129.2, 129.1, 128.9, 128.8, 128.4, 126.6, 126.5, 102.4, 102.3, 98.3, 98.2, 97.0, 79.1, 78.9, 78.6, 78.2, 77.6, 76.8, 75.8, 75.5, 75.4, 75.1, 73.5, 72.3, 68.9, 66.9, 60.3, 69.0, 60.0, 55.6; HRMS-ESI ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{49}\text{H}_{50}\text{O}_{18}\text{Na}$ , 949.2895; found, 949.2950.



#### 8.1.1.11. Methyl

*2,3,4-Tri-O-acetyl-6-O-(2-azido-3-O-benzyl-4,6-O-benzylidene-2-deoxy- $\beta$ -D-mannopyranosyl)- $\alpha$ -D-glucopyranoside and the  $\alpha$ -Anomer [Typical Protocol for the Thioglycoside/Sulfoxide Method] (**19**)*

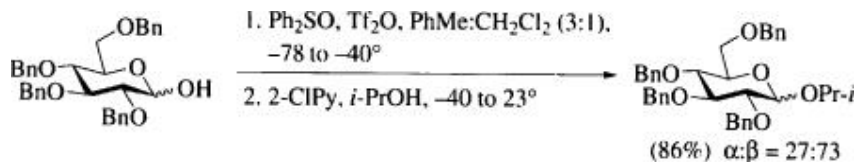
To a solution of S-phenyl

2-azido-3-O-benzyl-4,6-O-benzylidene-2-deoxy-1-thio- $\alpha$ -D-mannopyranoside (1.0 equiv),  $\text{Ph}_2\text{SO}$  (2.8 equiv), TTBP\* (3.0 equiv) in dichloromethane (4 mL) was added at  $-60^\circ$   $\text{Tf}_2\text{O}$  (1.4 equiv). The reaction mixture was stirred for 5 minutes, after which a solution of the methyl 2,3,4-tri-O-acetyl- $\alpha$ -D-glucopyranoside (1.5 equiv) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added. The mixture was stirred at  $-60^\circ$  for 1 hour, after which it was slowly warmed to room temperature and quenched by the addition of saturated aqueous  $\text{NaHCO}_3$ . The organic layer was washed with brine, dried ( $\text{MgSO}_4$ ), filtered and concentrated. The glycosides were isolated in a 4:1  $\beta : \alpha$  ratio in 93% combined yield by silica gel chromatography (EtOAc in petroleum ether).  $\beta$ -Anomer:  $R_f = 0.37$  (50% EtOAc in petroleum ether);  $[\alpha]_D^{25} + 6.8^\circ$  (c 1.2,



CHCl<sub>3</sub>); <sup>1</sup>H NMR ( CDCl<sub>3</sub>) δ 7.55–7.36 (m, 10H), 5.57 (s, 1H), 5.49 (t, *J* = 9.8 Hz, 1H), 4.82 (m, 5H), 4.57 (s, 1H), 4.29 (dd, *J* = 10.4, 4.8 Hz, 1H), 4.09 (m, 1H), 4.08 (dd, *J* = 10.6, 3.5 Hz, 1H), 4.00 (t, *J* = 10.0 Hz, 1H), 3.87 (t, *J* = 10.2 Hz, 1H), 3.73 (dd, *J* = 9.5, 3.7 Hz, 1H), 3.52 (dd, *J* = 10.6, 7.1 Hz, 1H), 4.43 (d, *J* = 10.5 Hz, 1H), 3.38 (s, 3H), 3.34 (m, 1H), 2.05 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H); <sup>13</sup>C NMR ( CDCl<sub>3</sub>) δ 170.1, 169.9, 169.6, 137.7, 137.2, 129.1, 129.0, 128.5, 128.2, 127.7, 125.9, 125.3, 125.2, 101.5, 100.7, 96.6, 78.3, 76.0, 72.9, 70.8, 69.9, 68.8, 68.7, 67.6, 55.3, 20.6; ESIMS (*m/z*): [M + Na]<sup>+</sup> 708.3.

α -Anomer: *R*<sub>f</sub> = 0.48 (50% EtOAc in petroleum ether); [α]<sub>D</sub><sup>25</sup> – 1.8° (*c* 0.5, CHCl<sub>3</sub>); <sup>1</sup>H NMR ( CDCl<sub>3</sub>) δ 7.55–7.36 (m, 10H), 5.60 (s, 1H), 5.46 (t, *J* = 9.7 Hz, 1H), 5.08 (t, *J* = 9.7 Hz, 1H), 4.90 (m, 3H), 4.80 (s, 1H), 4.74 (d, *J* = 8 Hz, 1H), 4.19 (dd, *J* = 10.1, 4.5 Hz, 1H), 4.10 (m, 2H), 3.92 (m, 2H), 3.81 (t, *J* = 10.4 Hz, 1H), 3.78 (m, 2H), 3.49 (d, *J* = 11.3 Hz, 1H), 3.35 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H); <sup>13</sup>C NMR ( CDCl<sub>3</sub>) δ 171.4, 170.8, 139.1, 137.2, 128.9, 128.8, 128.3, 128.2, 127.9, 126.3, 125.9, 125.6, 100.8, 99.9, 96.4, 78.2, 76.3, 72.7, 71.1, 70.0, 69.3, 69.0, 67.9, 55.1, 20.7; ESIMS (*m/z*): [M + Na]<sup>+</sup> 708.4.

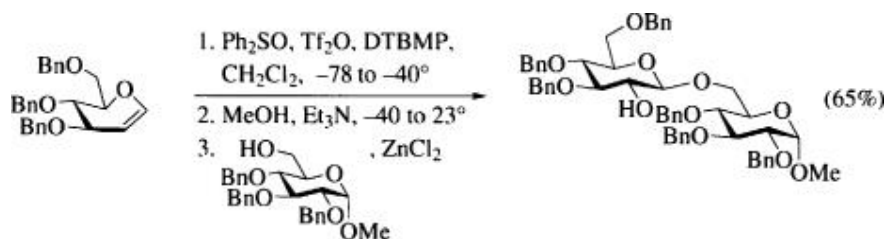


#### 8.1.1.12. Isopropyl 2,3,4,6-Tetra-O-benzyl-D-glucopyranoside [General Procedure for Dehydrative Glycosylation] (21)

Trifluoromethanesulfonic anhydride (45 μL, 0.27 mmol) was added to a solution of 2,3,4,6-tetra-O-benzyl-D-glucopyranose (103 mg, 0.191 mmol) and diphenyl sulfoxide (108 mg, 0.535 mmol) in a mixture of toluene and CH<sub>2</sub>Cl<sub>2</sub> (8 mL, 3:1 v/v) at –78°. The reaction mixture was stirred at this temperature for 5 minutes and then at –40° for 1 hour. 2-Chloropyridine (90 μL, 0.96 mmol) and isopropyl alcohol (44 μL, 0.57 mmol) were added sequentially at –40°. The solution was stirred at this temperature for 1 hour, then at 0° for 30 minutes, and finally at 23° for 1 hour before the addition of excess triethylamine (212 μL, 1.53 mmol). The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and was washed sequentially with saturated aqueous NaHCO<sub>3</sub> solution (2 × 100 mL) and saturated aqueous NaCl solution (100 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated, and the residue was purified by silica gel flash column chromatography (gradient elution: 9–30% EtOAc in hexane) to afford the title compound (197, 198) (95 mg, 86%; α : β = 27:73) as a white solid. Anal. Calcd for C<sub>37</sub>H<sub>42</sub>O<sub>6</sub>: C, 76.26; H, 7.26. Found (anomeric mixture): C, 76.57; H, 7.57. Analytical samples of each anomer were obtained by

preparative TLC (20% EtOAc in hexane).  $\alpha$ -Anomer: viscous oil;  $R_f = 0.43$  (33% EtOAc in hexane);  $[\alpha]_D^{20} + 28^\circ$  (c 0.4, CHCl<sub>3</sub>); FTIR (neat film) 3064, 3030, 2922, 1454, 1364, 1157, 1072, 1040, 1029, 1015 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.4–7.1 (m, 20H), 5.00 (d,  $J = 10.8$  Hz, 1H), 4.88 (d,  $J = 3.8$  Hz, 1H), 4.83 (d,  $J = 10.6$  Hz, 1H), 4.82 (d,  $J = 10.8$  Hz, 1H), 4.78 (d,  $J = 12.0$  Hz, 1H), 4.65 (d,  $J = 12.0$  Hz, 1H), 4.62 (d,  $J = 12.3$  Hz, 1H), 4.47 (d,  $J = 12.1$  Hz, 2H), 4.00 (t,  $J = 9.3$  Hz, 1H), 3.90 (m, 1H), 3.85 (ddd,  $J = 2.0, 3.4, 10.2$  Hz, 1H), 3.74 (dd,  $J = 3.6, 10.5$  Hz, 1H), 3.64 (m, 2H), 3.56 (dd,  $J = 3.8, 9.6$  Hz, 1H), 1.13 (d,  $J = 6.3$  Hz, 3H), 1.18 (d,  $J = 6.0$  Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  139.0, 138.3, 138.3, 138.0, 128.5, 128.4, 128.4, 128.2, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 94.8, 82.2, 79.9, 77.9, 75.7, 75.2, 73.5, 73.2, 70.0, 69.0, 68.5, 23.2, 21.2; HRMS-FAB ( $m/z$ ):  $[M - H]^+$  calcd for C<sub>37</sub>H<sub>41</sub>O<sub>6</sub>, 581.2903; found, 581.2903.

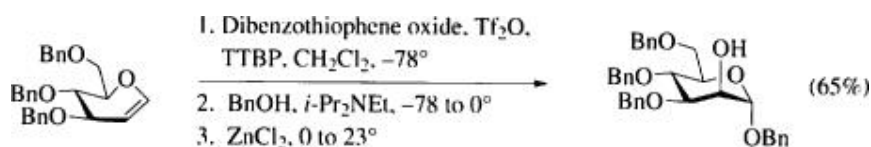
$\beta$ -Anomer: white solid, mp 105° (lit. mp 107–108°);  $R_f = 0.33$  (33% EtOAc in hexane);  $[\alpha]_D^{20} + 10^\circ$  (c 0.9, CHCl<sub>3</sub>) [lit.  $[\alpha]_D^{25} + 11^\circ$  (c 1, CDCl<sub>3</sub>)]; FTIR (neat film) 3031, 2904, 1454, 1121, 1104, 1069, 1039 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.4–7.1 (m, 20H), 5.00 (d,  $J = 11.0$  Hz, 1H), 4.95 (d,  $J = 10.9$  Hz, 1H), 4.84 (d,  $J = 11.1$  Hz, 1H), 4.81 (d,  $J = 10.8$  Hz, 1H), 4.73 (d,  $J = 10.9$  Hz, 1H), 4.63 (d,  $J = 12.3$  Hz, 1H), 4.59 (d,  $J = 11.1$  Hz, 1H), 4.57 (d,  $J = 10.8$  Hz, 1H), 4.50 (d,  $J = 7.8$  Hz, 1H), 4.05 (m, 1H), 3.76 (dd,  $J = 1.8, 10.8$  Hz, 1H), 3.70 (m, 1H), 3.58 (t,  $J = 9.6$  Hz, 1H), 3.48 (m, 1H), 3.46 (dd,  $J = 7.9, 9.1$  Hz, 1H), 1.34 (d,  $J = 6.2$  Hz, 3H), 1.27 (d,  $J = 6.2$  Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  138.7, 138.6, 138.4, 138.2, 128.4, 128.3, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 127.6, 102.2, 84.9, 82.4, 78.0, 75.7, 75.0, 74.9, 74.9, 73.5, 72.4, 69.2, 23.8, 22.3; HRMS-FAB ( $m/z$ ):  $[M - H]^+$  calcd for C<sub>37</sub>H<sub>41</sub>O<sub>6</sub>, 581.2903; found, 581.2903.



8.1.1.13. Methyl 6-O-(3,4,6-Tri-O-benzyl- $\beta$ -D-glucopyranosyl)-2,3,4-tri-O-benzyl- $\alpha$ -D-glucopyranoside [General Protocol for Oxidative  $\beta$ -Glucosylation of Glycals] (23)

Trifluoromethanesulfonic anhydride (61  $\mu$ L, 0.36 mmol) was added to a solution of tri-O-benzyl-D-glucal (100 mg, 0.2 mmol), diphenyl sulfoxide (146 mg, 0.7 mmol), and DTBMP (172 mg, 0.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at  $-78^\circ$ . The reaction mixture was stirred at this temperature for 30 minutes and then at  $-40^\circ$  for 1 hour. Methanol (10  $\mu$ L, 0.25 mmol) and triethylamine (100  $\mu$ L,

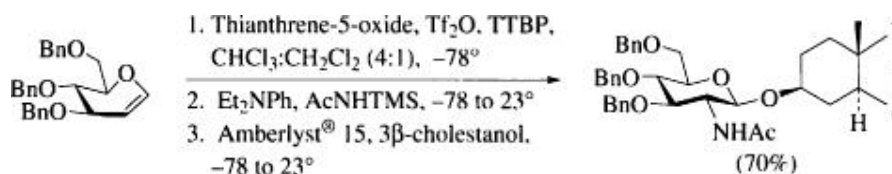
0.72 mmol) were added sequentially at  $-40^{\circ}$ . The solution was stirred at this temperature for 30 minutes, then at  $0^{\circ}$  for 1 hour and at  $23^{\circ}$  for 1 hour. A solution of methyl 2,3,4-tri-*O*-benzyl- $\alpha$ -D-glucopyranoside (250 mg, 0.54 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL) was added at  $0^{\circ}$ . Zinc chloride (480  $\mu\text{L}$ , 1.0 M in ether, 0.48 mmol) was added at  $-78^{\circ}$ , and the mixture was stirred at this temperature for 40 minutes, then at  $0^{\circ}$  for 1 hour and finally at  $23^{\circ}$  for 4 hours. The reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (15 mL) and washed sequentially with saturated aqueous sodium bicarbonate solution ( $2 \times 15$  mL) and saturated aqueous sodium chloride solution (10 mL). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated, and the residue was purified by silica gel flash column chromatography (25% EtOAc in benzene) to afford the title compound (140 mg, 65%) as a white solid, mp  $135$ – $136^{\circ}$  (methanol/benzene);  $R_f = 0.40$  (20% EtOAc in benzene);  $[\alpha]_D^{20} + 14.0^{\circ}$  ( $c$  1.2,  $\text{CHCl}_3$ ); FTIR (neat film) 3472, 3088, 3062, 3030, 2903, 2869, 1497, 1454, 1360, 1090, 1066, 1028  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.37–7.26 (m, 28H), 7.19–7.15 (m, 2H), 4.98 (d,  $J = 10.8$  Hz, 1H), 4.91 (d,  $J = 11.1$  Hz, 1H), 4.89 (d,  $J = 10.7$  Hz, 1H), 4.82 (d,  $J = 11.1$  Hz, 1H), 4.82 (d,  $J = 10.8$  Hz, 1H), 4.81 (d,  $J = 11.1$  Hz, 1H), 4.78 (d,  $J = 13.8$  Hz, 1H), 4.66 (d,  $J = 12.2$  Hz, 1H), 4.61 (d,  $J = 11.5$  Hz, 1H), 4.61 (d,  $J = 3.2$  Hz, 1H), 4.58 (d,  $J = 12.4$  Hz, 1H), 4.52 (d,  $J = 9.8$  Hz, 1H), 4.52 (d,  $J = 12.6$  Hz, 1H), 4.23 (d,  $J = 7.2$  Hz, 1H), 4.15 (dd,  $J = 2.2, 10.9$  Hz, 1H), 4.00 (t,  $J = 9.3$  Hz, 1H), 3.84–3.80 (m, 1H), 3.72 (dd,  $J = 1.9, 11.0$  Hz, 1H), 3.70–3.65 (m, 2H), 3.57–3.48 (m, 5H), 3.46–3.43 (m, 1H), 3.37 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  138.7, 138.6, 138.2, 138.2, 138.1, 138.0, 128.5, 128.4, 128.4, 128.4, 128.4, 128.2, 128.0, 128.0, 127.9, 127.8, 127.8, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 103.5, 98.1, 84.4, 82.0, 79.7, 78.0, 77.5, 75.8, 75.3, 75.1, 75.0, 75.0, 74.5, 73.4, 73.4, 69.8, 68.9, 68.8, 55.3; HRMS-FAB ( $m/z$ ):  $[\text{M} - \text{H}]^+$  calcd for  $\text{C}_{55}\text{H}_{59}\text{O}_{11}$ , 895.4057; found, 895.4056.



#### 8.1.1.14. Benzyl 3,4,6-Tri-*O*-benzyl- $\alpha$ -D-mannopyranoside [General Procedure for Oxidative Mannosylation of Glycals] (54)

To a solution of dibenzothiophene-5-oxide (0.24 g, 1.2 mmol) and TTBP (30 mg, 0.12 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) at  $-78^{\circ}$  was added trifluoromethanesulfonic anhydride (80  $\mu\text{L}$ , 0.48 mmol). The solution was stirred at  $-78^{\circ}$  for 10 minutes, then at  $-45^{\circ}$  for 1 hour before it was cooled back to  $-78^{\circ}$ . A solution of 3,4,6-tri-*O*-benzyl-D-glucal (94 mg, 0.23 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) at  $-78^{\circ}$  was added to the reaction vessel via cannula. The resulting solution was stirred at this temperature for 1 hour before the sequential

addition of benzyl alcohol (74  $\mu\text{L}$ , 0.72 mmol) and diisopropylethylamine (250  $\mu\text{L}$ , 1.4 mmol). The reaction mixture was stirred at  $-78^\circ$  for 15 minutes, then at  $-45^\circ$  for 15 minutes, and finally at  $0^\circ$  for 20 minutes before a solution of  $\text{ZnCl}_2$  in ether (1.0 M, 480  $\mu\text{L}$ , 0.48 mmol) was added. The reaction mixture was then stirred at  $0^\circ$  for 25 minutes and then at  $23^\circ$  for 16 hours. The solution was partitioned between  $\text{CH}_2\text{Cl}_2$  (15 mL) and water (15 mL), and the aqueous layer was further extracted with dichloromethane ( $3 \times 20$  mL). The combined organic layers were washed with water ( $3 \times 10$  mL) and dried ( $\text{Na}_2\text{SO}_4$ ). The filtrate was concentrated and the residue was purified by column chromatography (5% EtOAc in benzene) to afford the title compound (80 mg, 65%).  $R_f = 0.59$  (35% EtOAc in benzene); FTIR (neat film) 3452, 3063, 3031, 2916, 1644, 1496, 1454, 1364, 1209, 1056, 1028, 911, 801, 736, 698,  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.39–7.26 (m, 18H), 7.20–7.18 (m, 2H) 5.03 (d,  $J = 1.5$  Hz, 1H), 4.85 (d,  $J = 10.8$  Hz, 1H), 4.74 (d,  $J = 11.9$  Hz, 1H), 4.72 (d,  $J = 11.3$  Hz, 1H), 4.69 (d,  $J = 12.6$  Hz, 1H), 4.57 (d,  $J = 12.1$  Hz, 1H), 4.53 (d,  $J = 10.9$  Hz, 1H), 4.52 (d,  $J = 11.9$  Hz, 1H), 4.1 (dd,  $J = 1.8, 3.2$  Hz, 1H), 3.96 (dd,  $J = 3.1, 8.9$  Hz, 1H), 3.92 (t,  $J = 8.8, 9.7$  Hz, 1H), 3.88–3.86 (m, 1H), 3.79 (dd,  $J = 4.2, 10.6$  Hz, 1H), 3.72 (dd,  $J = 1.8, 10.7$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  164.7, 138.4, 138.4, 138.1, 138.0, 137.4, 128.7, 128.6, 128.6, 128.5, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 98.6, 80.5, 80.5, 77.5, 75.5, 75.4, 74.5, 74.5, 73.8, 73.6, 72.2, 71.6, 71.4, 69.3, 69.0, 68.6, 66.6; HRMS-FAB ( $m/z$ ):  $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{34}\text{H}_{36}\text{O}_6\text{Na}$ , 563.2410; found, 563.2408.



8.1.1.15. 3  $\beta$  -Cholestanyl 2-N-Acetylamino-3,4,6-tri-O-benzyl-2-deoxy-  $\beta$ -D-glucopyranoside [General Procedure for Acetamidoglycosylation of Glycals] (57)

Triflic anhydride (81  $\mu\text{L}$ , 0.48 mmol) was added to a solution of tri-O-benzyl-D-glucal (100 mg, 0.24 mmol) and thianthrene-5-oxide (112 mg, 0.48 mmol) in a mixture of  $\text{CHCl}_3$  and  $\text{CH}_2\text{Cl}_2$  (5 mL; 4:1) at  $-78^\circ$ . The reaction mixture was stirred at this temperature for 10 minutes, followed by the sequential addition of *N,N*-diethylaniline (152  $\mu\text{L}$ , 0.960 mmol) and solid *N*-TMS-acetamide (72 mg, 0.552 mmol). The reaction mixture was immediately warmed to  $23^\circ$  and was stirred at this temperature for 2 hours. The solution was cooled to  $-78^\circ$ , Amberlyst<sup>®</sup> – 15 (145 mg) and cholestanol (280 mg, 0.72 mmol) were added, and the mixture was then stirred at  $23^\circ$  for 17 hours. The reaction mixture was filtered, and the filtrate was partitioned

between CH<sub>2</sub>Cl<sub>2</sub> (80 mL) and saturated aqueous NaCl solution (100 mL). The aqueous phase was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (70 mL). The combined organic layers were dried ( Na<sub>2</sub>SO<sub>4</sub>) and concentrated, and the residue was purified by silica gel flash column chromatography to afford the title compound (144 mg, 70%) as a white solid, mp 176–177°; TLC (silica gel) *R*<sub>f</sub> = 0.39 (20% EtOAc in benzene); [α]<sub>D</sub><sup>20</sup> + 27.8° (*c* 1.0, CHCl<sub>3</sub>); FTIR (neat film) 3286, 3064, 3031, 2932, 2866, 1655, 557, 1496, 1453, 1373, 1311, 1118, 1072, 1027 cm<sup>-1</sup>; <sup>1</sup>H NMR ( CDCl<sub>3</sub>) δ 7.33–7.27 (m, 13H), 7.21–7.19 (m, 2H), 5.55 (d, *J* = 7.3 Hz, 1H), 5.01 (d, *J* = 8.0 Hz, 1H), 4.83 (d, *J* = 11.5 Hz, 1H), 4.79 (d, *J* = 11.0 Hz, 1H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.61 (d, *J* = 12.3 Hz, 1H), 4.58 (d, *J* = 10.9 Hz, 1H), 4.55 (d, *J* = 12.1 Hz, 1H), 4.26 (dd, *J* = 8.2, 9.9 Hz, 1H), 3.75 (dd, *J* = 1.7, 9.9 Hz, 1H), 3.68 (m, 1H) 3.56 (m, 3H), 3.18 (dt, *J* = 7.8, 9.9 Hz, 1H), 1.96 (m, 1H), 1.91–1.76 (m, 2H), 1.84 (m, 3H), 1.70–1.43 (m, 7H), 1.36–0.92 (m, 21H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 2.3 Hz, 3H), 0.85 (d, *J* = 2.5 Hz, 3H), 0.77 (s, 3H), 0.64 (s, 3H); <sup>13</sup>C NMR ( CDCl<sub>3</sub>) δ 170.4, 138.6, 138.3, 138.1, 128.5, 128.4, 128.3, 127.9, 127.9, 127.7, 127.7, 127.7, 127.6, 98.1, 80.3, 79.0, 78.8, 74.8, 74.7, 74.6, 73.4, 69.1, 58.2, 56.4, 56.2, 54.4, 44.6, 42.6, 40.0, 39.5, 37.0, 36.2, 35.8, 35.5, 35.4, 34.6, 32.1, 29.4, 28.8, 28.2, 28.0, 24.2, 23.8, 23.6, 22.8, 22.6, 21.2, 18.6, 12.3, 12.0; HRMS-FAB (*m/z*): [M + H]<sup>+</sup> calcd for C<sub>56</sub>H<sub>80</sub>NO<sub>6</sub>, 862.5986; found, 862.5988.

## 9. Tabular Survey

The literature was searched to the end of 2002 by Chemical Abstracts and citation searching. Later examples have been included as far as possible. No attempts were made to cover the patent literature. A dash enclosed in parentheses (–) indicates the yield was not reported. Failed reactions have not been included in the Tables as in many cases it is not obvious why they failed, other than perhaps for solubility reasons. (199)

In each Table the donors are listed alphabetically, for example, arabinose, fucose, galactose, glucose, etc. For each particular configuration of donor those carrying non-participating, arming protecting groups are listed first, followed by those with participating, disarming groups and finally those carrying cyclic protecting groups, such as benzylidene rings and bisacetals, which may be arming or disarming according to location. Deoxy and aminodeoxy donors are listed at the end of the stereochemical group from which they derive. In the acceptors, for each particular donor, non-carbohydrate aliphatic alcohols are listed first in order of increasing size. These are followed by phenols and acids and then by carbohydrates. The carbohydrate acceptors themselves, for each particular donor, are grouped into primary alcohols, usually 6-OH's, followed by secondary alcohols in the sequence 2-OH, 3-OH, 4-OH.

The following abbreviations are used in the Tables:

All	allyl
Alloc	allyloxycarbonyl
Ac	acetyl
BOM	benzyloxymethyl
Bn	benzyl
BSP	1-benzenesulfinylpiperidine
Bz	benzoyl
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
ClAc	chloroacetyl
2-CIPy	2-chloropyridine
DTBP	2,6-di- <i>tert</i> -butylpyridine
DTBMP	2,6-di- <i>tert</i> -butyl-4-methylpyridine
Fmoc	9-fluorenylmethoxycarbonyl
MPBT	S-(4-methoxyphenyl)benzenethiosulfinate

MS	molecular sieves
nd	not determined
PBB	<i>p</i> -bromobenzyl
PEG	polyethyleneglycol
PhthN	phthalimido
Piv	pivaloyl
PMB	<i>p</i> -methoxybenzyl
PMBz	<i>p</i> -methoxybenzoyl
PMP	<i>p</i> -methoxyphenyl
Py	pyridine
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
TES	triethylsilyl
Tf <sub>2</sub> O	trifluoromethanesulfonic anhydride
TfOH	trifluoromethanesulfonic acid
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Trt	triphenylmethyl
TTBP	2,4,6-tri- <i>tert</i> -butylpyridine
TTBP*	2,4,6-tri- <i>tert</i> -butylpyrimidine

**Table 1. Formation of Pyranosides by the Sulfoxide Method**

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**Table 2. Formation of Pyranosides by the Thioglycoside/Sulfinate Method**

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**Table 3. Formation of Pyranosides by the Dehydrative Method**

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**Table 4. Formation of Pyranosides by the Oxidative Method**

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**Table 5. Formation of Furanosides**

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**Table 6. Formation of Glycosides by Intramolecular Aglycone Delivery**

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**Table 7. Formation of *N*-Glycosides and Nucleosides**

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**Table 8. Formation of Thioglycosides**

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**Table 9. Polymer-supported Glycosidic Bond Formation**

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**Table 10. Miscellaneous Non-Carbohydrate Sulfoxide Couplings**

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