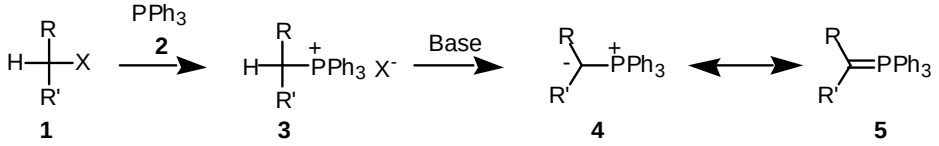
Chapter X. Olefinations

As ubiquitous features of natural products, unsaturated hydrocarbons are unquestionably important structures, demanding methodologies for their construction. For the synthetic chemist, carbon-carbon double and triple bonds are inviting handles for the conversion into other functional groups such as diols, epoxides, esters, aldehydes, and reduced hydrocarbons or translocation though sigmatropic rearrangements. Many of the tools for constructing olefins have evolved into powerful methods for fragmentation coupling primarily carbonyl condensation and elimination reactions.

The Wittig and Related reactions.

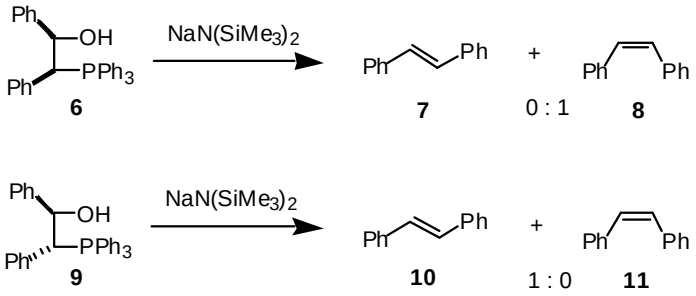
The Wittig reaction and several closely related processes are among the most powerful methods for coupling reactions through a ketone or aldehyde functionality. The active olefination reagent in the Wittig reaction is a phosphonium ylide **4** prepared by alkylation of an alkylhalide or similar electrophile with triphenyphosphine. With a pKa of about 23 in DMSO any suitable base, such as *n*-BuLi, NaH, LDA and *t*BuOK will convert the phosphonium salt to the phosphonium ylide (or phosphorane). Addition of an aliphatic aldehyde to the phosphorane gives the olefin with good levels of cis-selectivity.



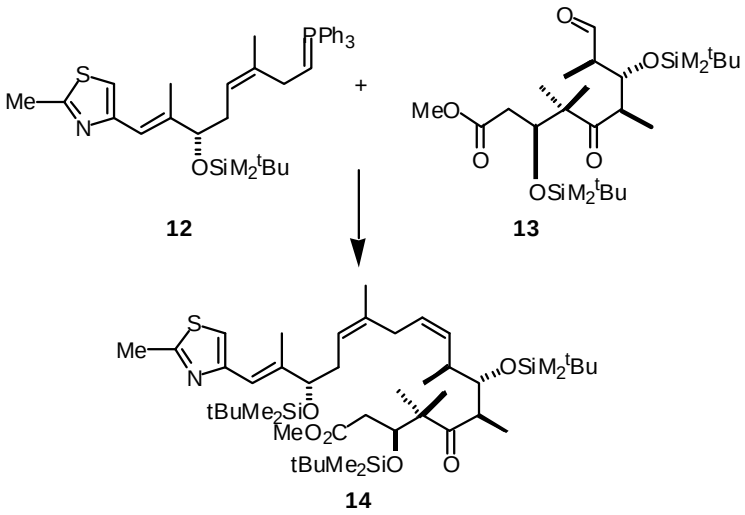
X = Cl, Br, I, OTs, etc.
R = Alkyl, R' = Alkyl, H

The stereochemistry of the reaction depends on the aldehyde (aliphatic vs. aromatic), the salts present in the reaction and resonance stabilization of the phosphorane. The selection of the electrophile in step on is important because the salts present in the reaction mixture affect the stereochemistry. In this regard, improved stereochemistry can often be realized by performing the reaction under salt-free conditions after precipitation under appropriate conditions.[1] For example, preparing the phosphorane in THF assists in the precipitation of NaCl, and toluene will help remove most KBr.

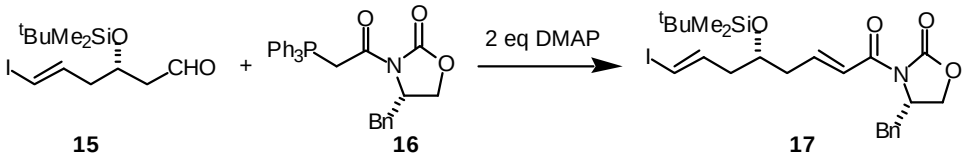
The cis selectivity of the reaction decreases with aromatic aldehydes, an observation that can be rationalized by reversal of the addition step. Emperical investigations showed that the decomposition of phosphatanes **6** and **9** are stereospecific leading to trans or cis products.[2] Recent theoretical calculations suggest that the reaction proceeds by a 2+2 mechanism directly to the oxaphosphatane and mechanistic debates about this reaction continues.



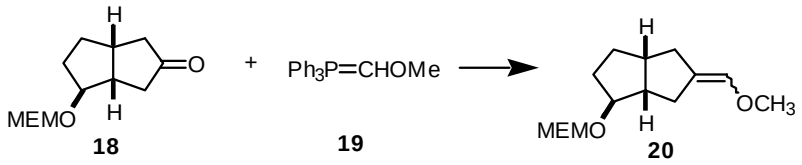
A few examples illustrate the power of the Wittig coupling reaction in total synthesis. During his studies on the epothilones, White achieved the cis selective formation of **14**.[3] Note that the ylide portion contains an acidic methyl group on the thiazole and the aldehyde is tethered to a β-silyloxy ester that could be prone to eliminate.



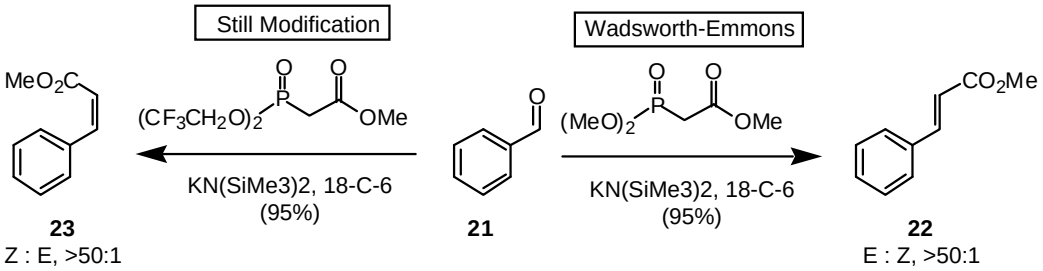
During synthetic studies for the synthesis of lepicin the Evans group employed a stabilized ylide derived from oxazolidinone **16**. Utilizing two equivalents of DMAP, the sensitive vinyl iodide **17** was secured as a 96 : 4 E : Z of olefins in 84% yield. Their investigations suggest that the selectivity in the initial condensation is 1.5 : 1 in favor of the E isomer, but equilibration via conjugate addition of the DMAP resulted in a substantially improved ratio of the E isomer.



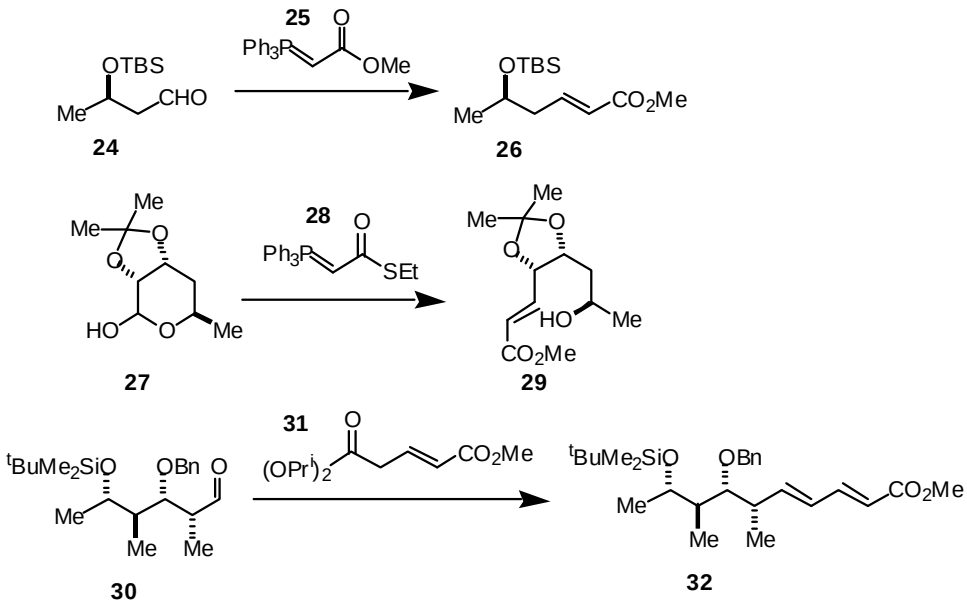
The incorporation of hetereoatoms on the alpha-position of the phosphonium ylide can be a useful tool for functional group homologation. The methoxymethylene ylide **19** provided a direct route to aldehydes after hydrolysis of the vinyl ether **20**.[4]



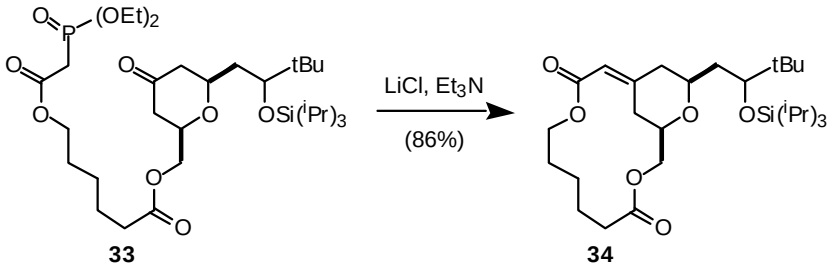
As noted, increasing the resonance stabilization of the phosphonium ylide in Witting reactions resulted in a marked deterioration of cis selectivity. Designing reagents with substantial stabilization of the ylide lead to predominantly trans olefins. The approach, known as the Horner reaction, works well when the ylide is stabilized by electron withdrawing groups, such as CN, SR, Ph or CO_2R. With an ester, the reactions is specifically known as the Wadsworth-Emmons reaction and provides excellent levels of selectivity for trans isomer, often exceeding >50 : 1. A modification of the Horner-Emmons-Wadsworth reaction by Still gives exclusively the cis isomer.[5]



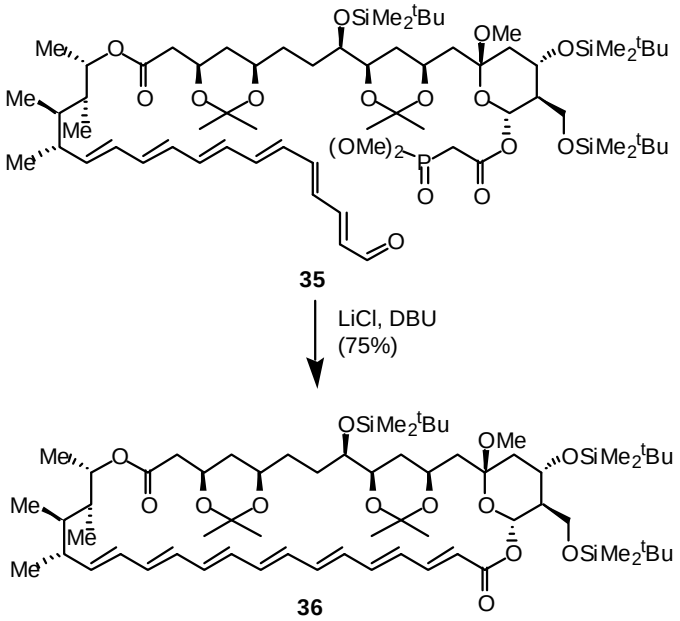
A remarkable feature of stabilized ylides (and also true for Wittig reagents) is that their weak basicity allows high yielding reactions with substrates that might be prone to β-elimination when treated with base, such as the β-silyloxy aldehyde **24**.[6] Strong bases are not required for deprotonation of stablilized ylides, and tertiary amines in the presence of added LiCl readily effect deprotonation.[7,8] The weakly basic character of stabilized ylides permits their use in the presence of free hydroxyl groups, and carbohydrate derived hemi-acetals **29** are cleanly converted into their linear structures.[9] Ylides stabilized by more remote vinylic esters such as **31** also show a propensity for formation of the trans isomer.[10,11]



Intramolecular olefinations with stabilized ylides are effective methods for the construction of macrocyclic ring systems. For example, in synthetic studies towards the synthesis of the bryostatins, Evans and Carreira reported the formation of macrocyclic lactone **34** by the use of an tethered Horner-Wadsworth-Emmons reaction.[12]

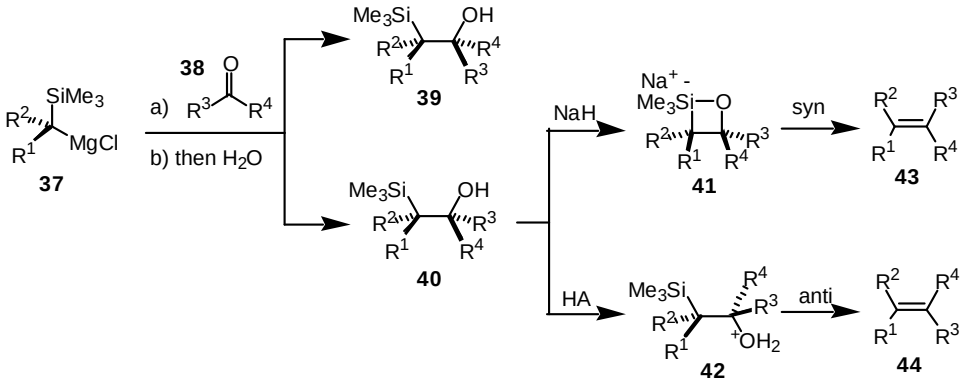


An equally impressive closure of the 36-membered ring **36** was achieved by Nicolaou and co-workers during synthetic studies of amphotericin and analogs.[13]

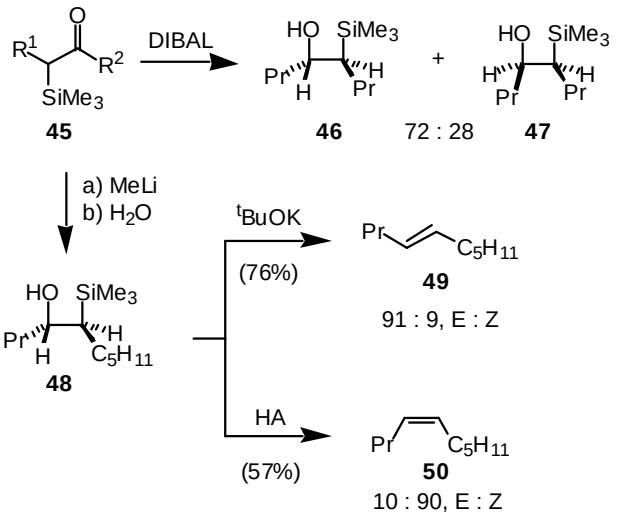


Peterson Olefination Reaction.

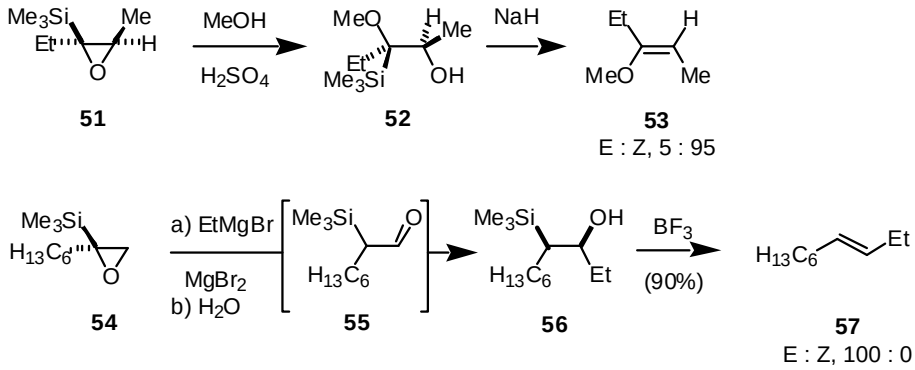
The Peterson olefination reaction is an effective means for creating carbon-carbon double bonds from ketones or aldehydes by the use of α-silyl carbanions **37**.[14] Although the exact mechanism remains unclear, β-alkoxy silane intermediates undergo stereospecific syn-elimination. With strongly coordinated counter ions such as Li, MgX or AlX_2, the elimination is slow and the intermediate, namely the β-alkoxy silane, can be protonated and the resulting β-hydroxy silanes **39** or **40** can be isolated. However, with more ionic Na^+ or K^+ counterions the reaction proceeds rapidly to olefinic product. When treated with base the β-hydroxy silane **40** undergoes a stereospecific syn elimination, presumably through a pentavalent silicon species **41**, to generate olefin **43**. When the same β-hydroxy silane is treated with acid the products are consistent with an anti elimination (**42** to **44**). An impressive feature of the Peterson olefination is that regardless of the stereochemistry of the product from the initial coupling between the α-silyl anion **37** and the carbonyl species **38**, either double bond isomer can be selectively from either β-hydroxysilyl intermediate.[15] For isolation of the β-hydroxy silanes **39** or **40**, both R^1 and R^2 must be electron donatating groups (alkyl, hydrogen) but not aromatic.



The β-hydroxy silanes can be generated from a variety of methods including addition of $BrMgCH_2SiMe_3$ to carbonyls. Additionally, α-silyl ketones are good Peterson precursors, with hydroxy formation available through the reduction of the ketone with DIBAL or addition of a carbanion (**XX**).[16,17] As before, either the cis or trans olefin **49** or **50** may be accessed from the same β-hydroxy silane.

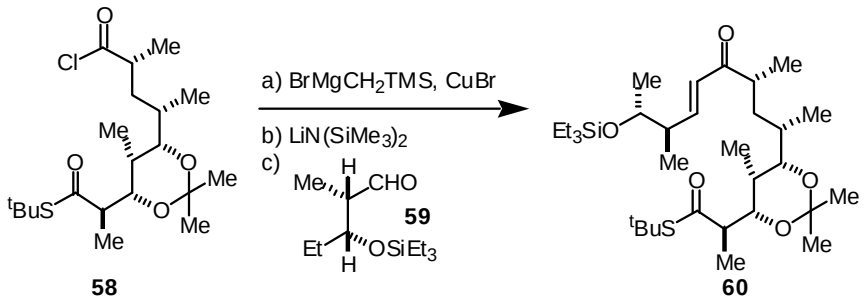


Additional sources for β-hydoxy silanes for the Peterson Olefination include 1-silylepoxides (**51**). Under acidic conditions, such as methanol with catalytic sulfuric acid, the methanol attacks the α-silyl carbon to give the β-hydroxy silane **53**, which when treated with sodium hydride provides the Z olefin **53** with 95 : 5 selectivity.[18,19] When treated with Grignard reagents in the presence of added $MgBr_2$, silyl epoxides, such as **54,** undergo a rearrangement to the aldehyde prior to Grignard addition. When **56** was treated with a BF_3•OEt2, anti elimination provided exclusively the E isomer in 90% yield.[20]



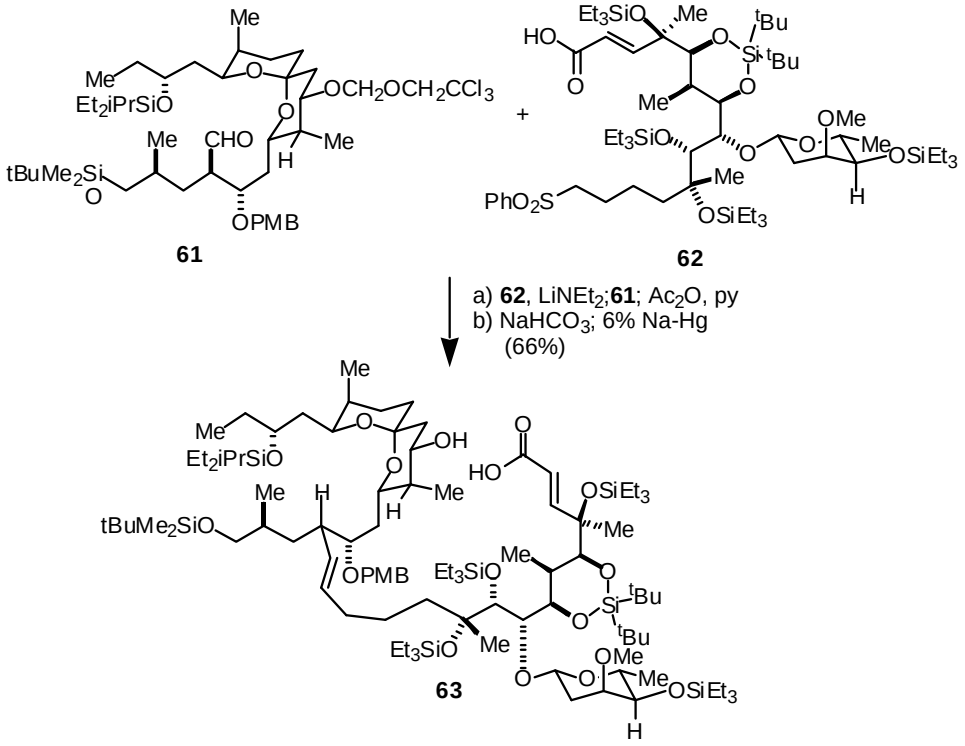
The total synthesis of norbonolide by Masamune beautifully illustrated the usefulness of α-trimethylsilyl ketones as Peterson olefination precursors,[21] despite the instability of these species.[22] The acid chloride **58** was converted to the α-silyl ketone by cuprate addition and immediately subjected to enolization with $LiN(SiMe_3)_2$ before the addition of aldehyde **59**. The intermediate b-alkoxy

silane is not isolated but is allowed to eliminate to the olefin. The entire sequence afforded the conjugated ketone **60** in 95% yield.

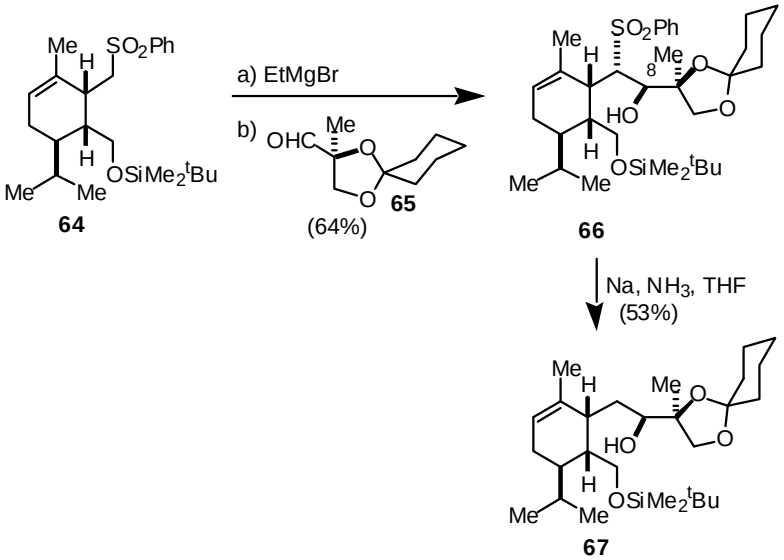


Julia Olefination Reaction.

The Julia reaction has been used successfully in numerous syntheses for the coupling of two structurally complicated molecular fragments.[23,24] The total synthesis of cytovaricin by Evans and coworkers illustrates the usefulness of the Julia coupling reaction.[25] In the synthesis, sulfone **62** was deprotonated and treated with aldehyde **61** to afford an intermediate alcohol. Acylation of the crude product permits facile elimination during reduction of the sulfone with sodium amalgam.



The condensation of an alkyl sulfone and an aldehyde under Julia conditions need not necessarily lead to formation of an olefin. For example, in synthetic studies on eleutherobin, Magnus coupled sulfone **64** with aldehyde **65** to provide **66** as a 10 : 1 mixture of diastereomers at C8 in 64% yield.[26] Without acetylation or protection of the alcohol at C8 its propensity to eliminate was reduced and selective reduction of the sulfone to **67** (without elimination of the C8 hydroxyl) was achieved with sodium in liquid ammonia.

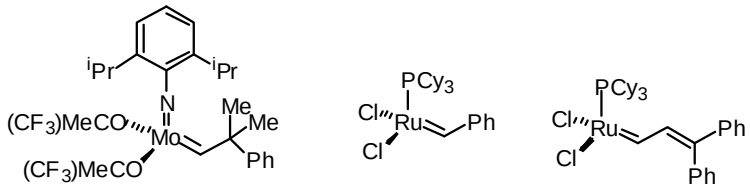


Olefin Metathesis.

The single greatest advancement in the last decade in the preparation of olefins is the development olefin metathesis catalysts that are functional group

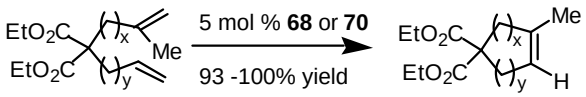
tolerant and remarkably efficient. Dozens of investigators are exploring the utility of metathesis catalysts in synthetic organic chemistry. The classes of reactions promoted by metathesis catalysts fall into three general categories, ring closing metathesis (RCM), ring opening metathesis (ROMP) and olefin cross metathesis (CM). Ring closing metathesis has received the greatest attention from synthetic chemists, but cross coupling metathesis is becoming increasingly reliable.

Although many transition metal complexes initiate olefin metathesis,[2728] the exact nature of the active catalysts has remained obscured until recently, when several structurally well-defined catalysts emerged. The three most important of these catalysts are those from the groups of Schrock (**68**) and Grubbs[29] (**69**-**70**).

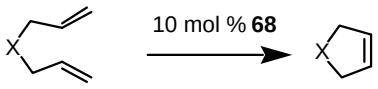


68 **69** **70**

The ruthenium based catalyts are tolerant of many functional groups and are not affected by air or water. In fact, water-soluble metathesis catalysts have been developed.[30] These metathesis catalysts are capable of effecting ring closing metathesis reactions for the creation of cycloalkanes from 5-membered rings up through large macrocycles. Both terminal and substituted olefins participate in the reaction, leading to cycloalkanes **72**,[31] furans[32] and pyrroles[32].



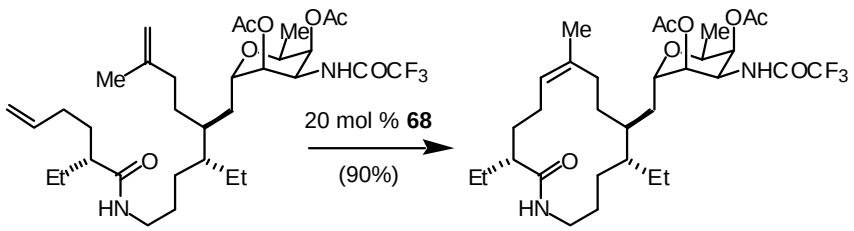
71, x, y = 1, 2, 3 **72**



73, X = O
75, X = NH

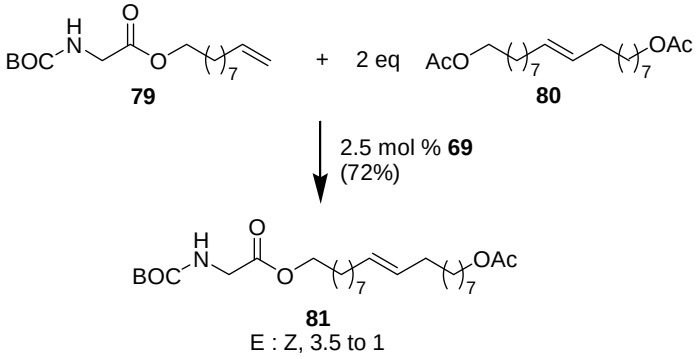
74 (99%)
76 (82%)

In the arena of macrocyclizations, ring closing metathesis has emerged as one of the most powerful methods available for effecting macrocylic ring formation. In the total synthesis of the antifungal agent Sch 38516 Hoveyda and coworkers assembled the macrocyclic lactam **77** in an impressive 90% by RCM.[33] In some instances, the catalyst **68** has proven to be more tolerable for olefin substitution that the Ru based catalysts.



77 **78**

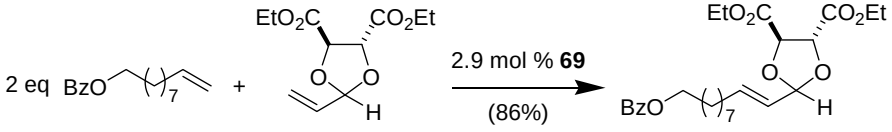
Olefin cross metathesis, or the intermolecular coupling between two identical or different olefins developed more slowly than RCM due to lower yields and cis/trans isomers. However, the metathesis catalyst **69** is effective for cross metathesis and provided predominately trans isomers in the olefin CM reaction of terminal olefins and a symmetrical disubstituted olefin. In the CM reaction of XX, the optimized procedure requires that equivalents of the disubstituted olefin XX are used.



79 **80**

81
E : Z, 3.5 to 1

The CM of two terminal alkenes worked well when two equivalents of the more sterically bulky of the two alkens was used. In the CM reaction of the terminal olefin **82** and the tartrate derived ketal **83**, the product **84** was obtained with good E : Z selectivity of 6.7 to 1 in 86% yield.



82 **83** **84**
E : Z, 6.7 : 1

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