Chapter 1

INTRODUCTION

Significant research efforts in the field of transition metal catalysis have led to the development of powerful methods for the formation of C–C and C–heteroatom bonds. Appropriate design of the catalyst and reaction conditions, along with careful choice of the substrate, can enable new and challenging transformations to proceed in high yield and selectivity. In this thesis, three categories of such transformations are presented: cross-coupling reactions to form carbon–silicon bonds, aldehyde-selective Wacker oxidations of fluorinated olefins, and olefin metathesis catalyzed by aminophosphine-ligated ruthenium complexes.

Nickel-catalyzed cross-coupling has proven to be a very effective strategy for the addition of organometallic reagents to unactivated alkyl electrophiles. In particular, secondary alkyl halides are useful coupling partners, despite previously being considered to exhibit poor reactivity in comparison to aryl and alkenyl electrophiles, due to challenging oxidative addition and competitive β-hydride elimination. While this class of reactions has predominantly been applied to the formation of C–C bonds, the extension of this strategy to the formation of C–B bonds presented by Fu and coworkers inspired the work presented in the second chapter of this thesis, which details the development of a nickel-catalyzed cross-coupling reaction of unactivated alkyl bromides and silylzinc nucleophiles, resulting in C–Si bond formation. A brief overview of established strategies to form C–Si bonds, as well as some of the current challenges, is discussed.

The palladium-catalyzed Wacker oxidation is a powerful tool for the oxidation of terminal olefins. However, controlling the regioselectivity of this process (i.e. whether C–O bond formation occurs at the internal position to produce a ketone or at the terminal position to produce an aldehyde) has been a longstanding challenge. Recent studies have led to new methods that promote Wacker oxidations that afford either ketones or aldehydes with good regioselectivity, and the investigation of new substrate classes has expanded the applications of this reaction to olefins bearing diverse functional groups. In the third chapter of this thesis, the nitrite-modified Wacker oxidation of allylic fluorides to selectively produce β-fluorinated

aldehydes is presented. Related methodologies developed for regioselective Wacker oxidation are discussed in this chapter.

The final chapter of this thesis describes kinetics and computational studies of new second-generation ruthenium olefin metathesis catalysts bearing aminophosphine ligands. Olefin metathesis has become an extremely important reaction in laboratory and industrial syntheses of substituted olefins and polymers. A comprehensive understanding of the effects of ligand composition and structure is valuable for the design of efficient and highly active catalysts. Background research related to the development of ruthenium olefin metathesis catalysts and examples of ligands that have been studied are described.

The research projects presented in this thesis, while diverse in nature, are aimed at improving catalyst selectivity and reactivity to open doors to new substrate classes and applications. These studies are expected to aide in the design of new coupling partners in challenging bond formations, reaction conditions to enhance catalyst selectivity, and ligands for controlling catalyst activity.

Strategies for Carbon–Silicon Bond Formation

Silicon-containing organic molecules have traditionally served as important intermediates in natural product total synthesis,[1] since C–Si bonds have the ability to be transformed into a variety of C–C and C–heteroatom bonds.[2] More recently, organosilicon molecules have been studied as analogs for their carbon-containing counterparts.[3] Silicon bioisosterism involves the incorporation of silicon atoms in place of carbon, with the potential to chemically affect drug targets by bestowing candidate molecules with specific chemical properties. There are several properties of silicon which make its replacement of carbon a powerful tool to tune the toxicity and activity of potential drugs: 1) larger covalent radius, 2) increased lipophilicity and, therefore, cellular uptake, and 3) enhanced hydrogen-bonding.[3] Additionally, silicon does not introduce any intrinsic toxicity, and cellular profiling studies of organosilicons[4] as well as the synthesis of silicon-containing drug analogs[5] and non-natural amino acids[6] have shown the potential of this synthetic strategy toward new drug targets (Figure 1.1).

The chemistry of allylsilanes has long been utilized in traditional organic synthesis.[7,8] For this reason, many methods have been established for the formation of allylsilanes. However, organic transformations of unactivated alkylsilanes remain far less explored. While reactions such as hydrosilylation and conjugate addition strategies have been extensively investigated, regioselective silylation reactions are limited to certain classes of substrates. Furthermore, sterically hindered starting materials are challenging substrates in current methodology, and alternate paths to synthesize tertiary alkylsilanes with broad substrate scope are rare.

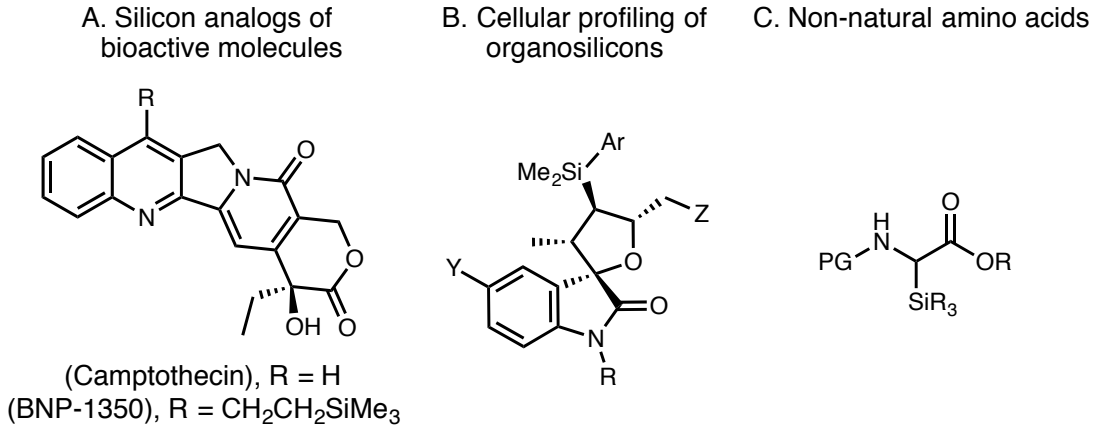


Figure 1.1. Biologically active compounds containing silicon.

The most established catalytic silylation reactions involve addition to unsaturated carbon–carbon bonds, via hydrosilylation[9-11] of olefins, conjugate addition[12-14] to α,β-unsaturated ketones, or silyl metalation and addition to olefins[15] (Figure 1.2). The field of hydrosilylation is well-developed and has important industrial use;[9] however, regioselectivity issues inherent to olefin addition remain. Furthermore, conjugate addition restricts substrate structure to α,β-unsaturated carbonyl compounds to form β-silyl products.

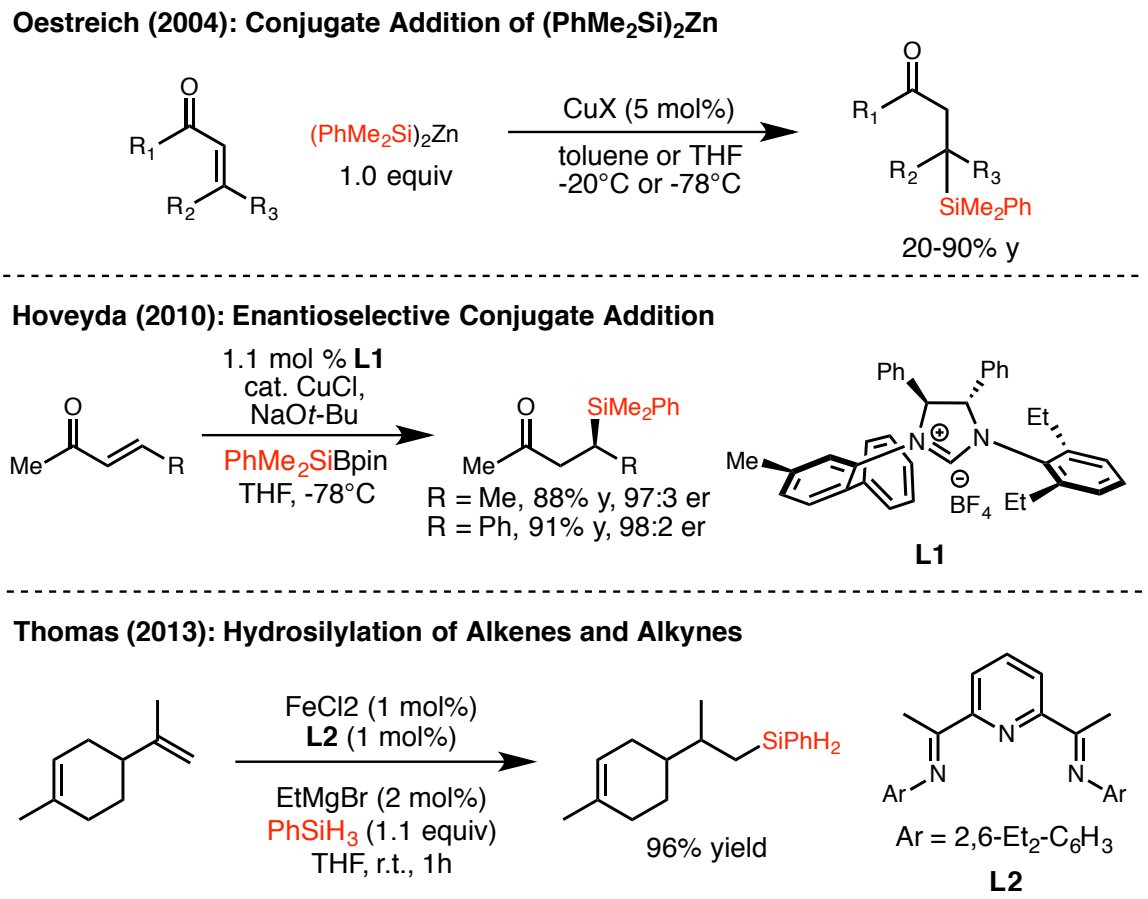


Figure 1.2. Established approaches for C–Si bond formation.

Copper, palladium, and nickel-catalyzed processes have been described for the silylative coupling of activated alkyl halides, including allylic, benzylic, and propargylic chlorides.[16-23] In 1980, Calas reported the cross-coupling of allylic and benzylic chlorides with disilanes catalyzed by $NiCp_2$.[17] Soon after, Nagai and coworkers published the Pd-catalyzed cross-coupling of benzylic chlorides to form dichloromethyl silanes.[18] The Oestreich group has worked extensively with silylative cross-coupling reactions,[16] employing both silylboron and disilylzinc nucleophiles to couple with allylic[19] and propargylic[20] alkyl chlorides. However, few cross-couplings of unactivated alkyl halides have been reported. The method described by Eaborn shown in Figure 1.3 is severely limited by sterics and does not display good functional group tolerance.[21] Thus, the cross-coupling of unactivated alkyl halides, especially of secondary and tertiary halides, to form C–Si bonds remains a challenging problem. The development of reaction conditions to address this challenge is presented in Chapter 2.

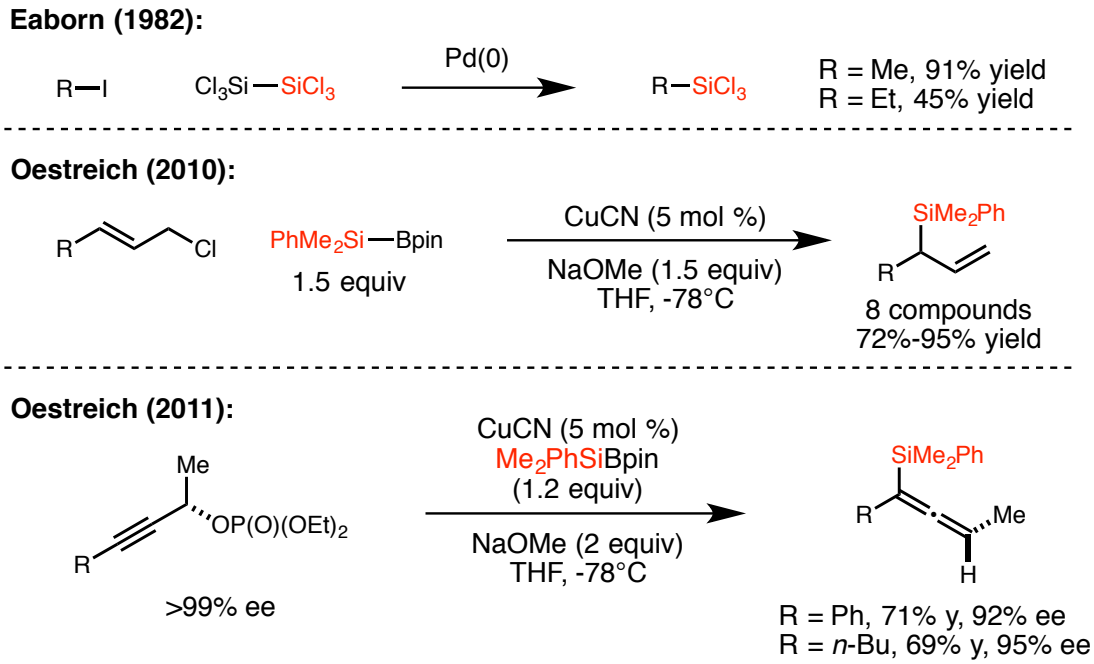
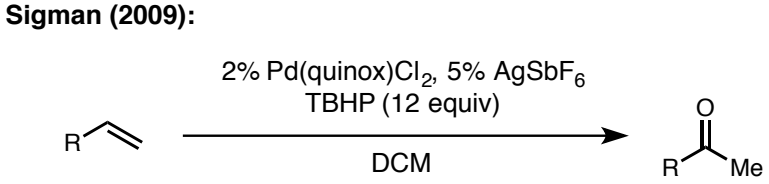


Figure 1.3. Cross-coupling strategies for C–Si bond formation.

Regioselectivity of the Wacker Oxidation

The Tsuji-Wacker oxidation is a widely-used reaction in the laboratory setting for the conversion of terminal olefins to methyl ketones.[24] However, although oxidation of terminal olefins is typically expected to proceed in accordance with Markovnikov's rule to form methyl ketones, the presence of proximal functional groups can lead to poor regioselectivity of oxidation. More recently, methods have been developed that promote selective oxidation of terminal olefins bearing substituents with a variety of electronic properties.

In 2009, Sigman and coworkers developed the ketone-selective peroxide-mediated oxidation of terminal olefins enabled by a palladium catalyst bearing a bidentate Quinox ligand (Scheme 1.1).[25]

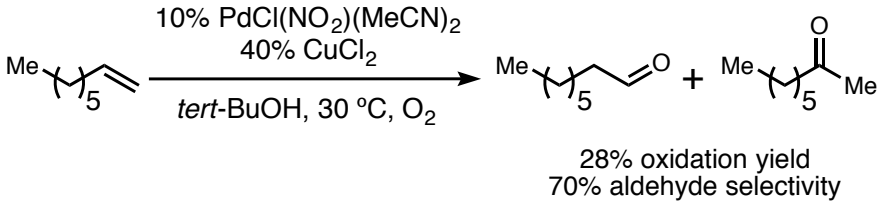


Scheme 1.1 Ketone-selective Wacker oxidation reported by Sigman.

This system provides high ketone yields for a broad scope of protected allylic alcohols and simple olefins.

In comparison to ketone-selective oxidations, the development of an aldehyde-selective Wacker oxidation has proven more elusive. Over the past few years, work by the Grubbs[26] and Feringa[27] groups has demonstrated aldehyde selectivity in the presence of a broad scope of functional groups. This work has been inspired by preliminary work reported by Feringa in the 1980s, in which a palladium nitrite catalyst provides modest aldehyde selectivity with the use of *tert*-butanol as the solvent (Scheme 1.2).[28] However, this reaction was limited by low oxidation yield.

Feringa (1986):



Scheme 1.2 Aldehyde-selective Wacker oxidation reported by Feringa.

Recently, the Grubbs group has significantly enhanced the aldehyde selectivity of this reaction through the use of a separate nitrite cocatalyst and a *tert*-butanol/nitromethane cosolvent system (Figure 1.4). These reaction conditions provide high yields and selectivity for both unbiased olefins as well as a variety of protected homoallylic alcohols.[26] Furthermore, isotope labeling experiments with ^{18}O-labeled nitrite, which show incorporation of ^{18}O from the nitrite salt in the carbonyl oxygen, have suggested that anti-Markovnikov addition of an NO_2 radical could be the cause of aldehyde selectivity under these reaction conditions.[26a] These mechanistic experiments provided insight into the origin of anti-Markovnikov addition in nitrite-modified Wacker oxidations, and are expected to guide future studies to expand the substrate scope of aldehyde-selective oxidations of diverse olefins. However, despite these advances, the reaction scope, particularly in relation to functional groups tolerated at the allylic position of the olefin,[29] remains limited. In a step toward overcoming this challenge, the development of reaction conditions for the anti-

Markonivkov oxidation of allylic fluorides to produce β-fluorinated aldehydes is presented in Chapter 3.

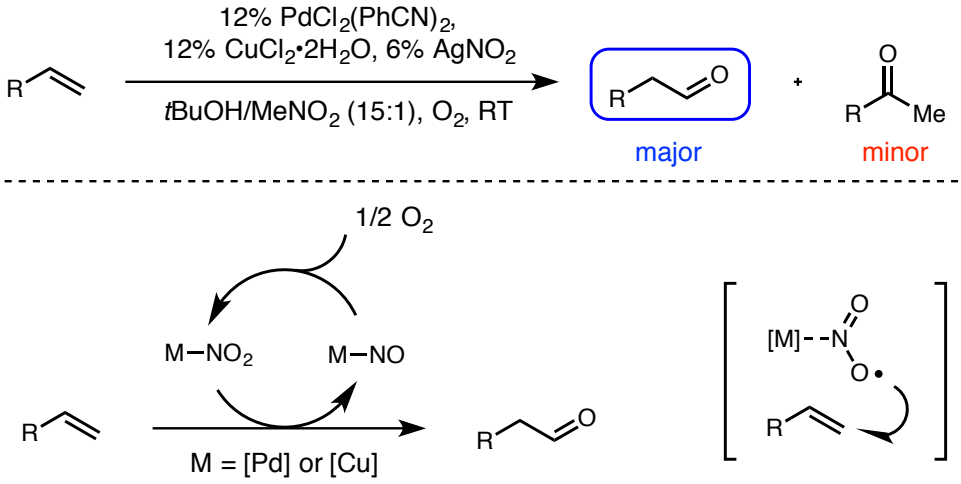


Figure 1.4. Proposed pathway leading to aldehyde selectivity in nitrite-modified Wacker oxidations reported by Grubbs and coworkers.

Ligand Effects on Ruthenium Olefin Metathesis Catalyst Activity

Ruthenium olefin metathesis catalysts have been widely used for their stability to air and moisture and high functional group tolerance. This strategy for the formation of carbon–carbon bonds has been applied extensively to the synthesis of small molecules and polymers in both laboratory and industrial settings. In the early 1990s, Grubbs reported the first well-defined ruthenium alkylidene catalysts (Figure 1.5).[30] This discovery soon led to the development of the ruthenium benzylidene complex referred to as the first-generation Grubbs catalyst (Figure 1.5).[31]

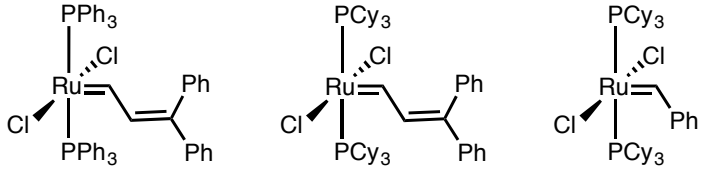


Figure 1.5. Early ruthenium olefin metathesis catalysts.

Despite the ease of use associated with ruthenium-based catalysts, the reactivities of the complexes shown in Figure 1.5 are low in comparison to early molybdenum olefin

metathesis catalysts. It was soon discovered that substitution of one of the phosphine ligands for an N-heterocyclic carbene (NHC) ligand dramatically increased ruthenium catalyst activity (Figure 1.6).[32] Examples of such catalysts include saturated and unsaturated NHC backbones. Furthermore, Hoveyda and coworkers reported ruthenium catalysts bearing chelating benzylidenes that exhibit increased stability.[33] Catalysts bearing two pyridine ligands have been shown to be particularly well suited for producing polymers by ring-opening metathesis polymerization (ROMP) with controlled molecular weights.[34]

Mechanistic studies of NHC-ligated ruthenium catalysts have revealed important information related to substituent effects of the phosphine ligand.[35] A number of arylphosphines containing phenyl substituents with varied electronic properties were compared in kinetics studies; these experiments showed that rates of phosphine dissociation (the catalyst initiation rates) correlate well with the donor strength of the phosphine ligand.[35b]

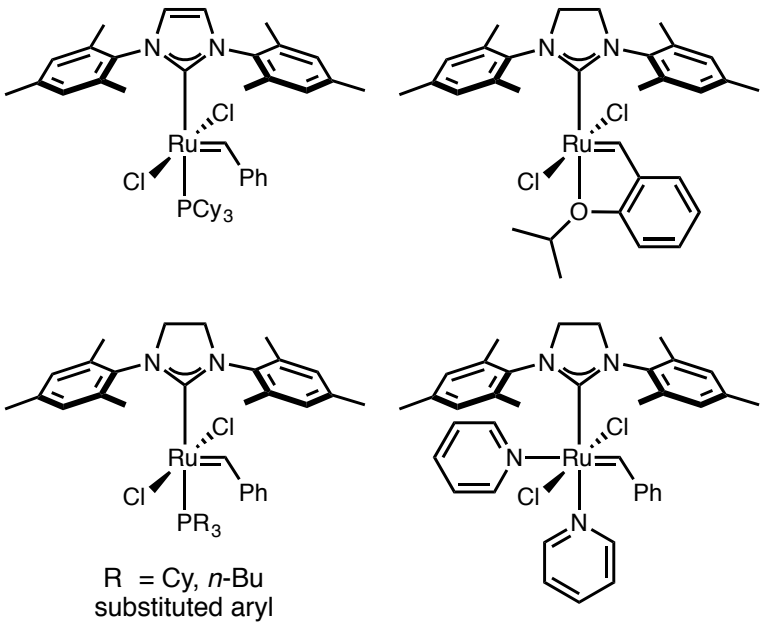


Figure 1.6. Examples of olefin metathesis catalysts bearing NHC ligands.

Phosphine ligands that have been used in second-generation ruthenium metathesis catalysts have predominantly contained three equivalent alkyl or aryl groups. Chapter 4 describes research involving ruthenium catalysts bearing phosphine ligands that contain incongruent substituents and P–X bonds, thereby expanding our understanding of ligand

effects on catalyst activity and potentially allowing access to new useful substrates for metathesis.

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