

Chapter 1

INTRODUCTION

1.1. Transition metal-catalyzed nucleophilic substitution reactions

With regard to retrosynthetic analysis, the nucleophilic substitution of an alkyl electrophile is a straightforward and efficient strategy in organic synthesis. However, classical methods like the S_N1 and S_N2 reactions have considerable limitations (**Figure 1.1**). The S_N1 reaction proceeds through the formation of a carbocationic intermediate, typically limiting the scope to tertiary and activated (e.g., benzylic or allylic) electrophiles. The scope of suitable nucleophiles is often limited by the requirement of a Brønsted or Lewis acid to facilitate dissociation of the leaving group. Finally, capture of the carbocation by the nucleophile often competes with side reactions, such as elimination to form an olefin and hydride / alkyl rearrangements (**Figure 1.1a**). The S_N2 reaction has similar limitations. It is sensitive to steric demands on the nucleophile and electrophile, rendering the method inapplicable to tertiary, many secondary, and hindered primary (e.g., neopentyl) electrophiles. Elimination also competes with substitution in the S_N2 reaction, as it is usually carried out under Brønsted-basic conditions (**Figure 1.1b**).¹

Classical nucleophilic substitution reactions also suffer from their difficulty in controlling the stereochemistry at the carbon undergoing substitution. Formation of an

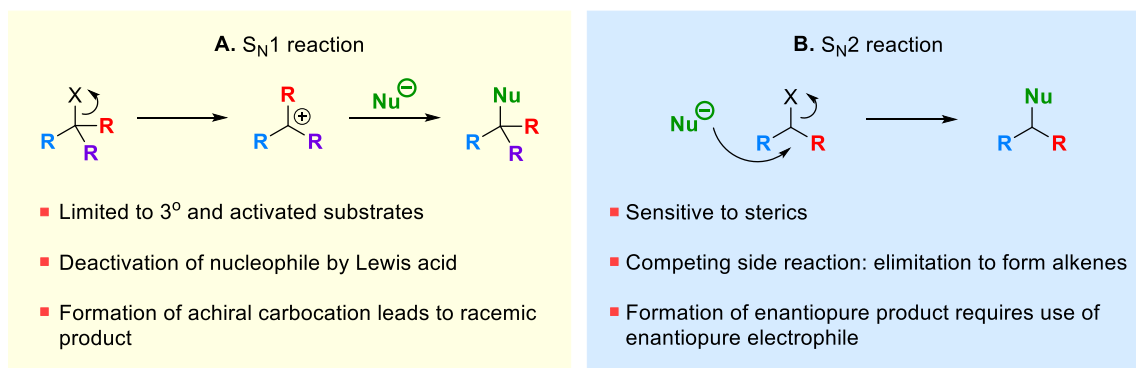


Figure 1.1. Limitations of classical nucleophilic substitution reactions (S_N1 and S_N2).

achiral carbocation typically leads to racemic product in the S_N1 reaction,² and in the case of the S_N2 reaction, the inversion of stereochemistry at the carbon center undergoing substitution means that the use of an enantioenriched electrophile is necessary for the formation of enantioenriched product. Due to these limitations, expanding the scope of nucleophilic substitution reactions, while simultaneously controlling the stereoselectivity of these processes, is a significant and ongoing goal in organic chemistry.

Transition metal-catalyzed cross-coupling has provided an exceptionally powerful approach to carbon-carbon bond formation, allowing chemists to solve a number of important problems in organic synthesis.³ Early studies of such processes mainly involved the use of palladium catalysts to generate a bond between two sp^2 -hybridized carbons, a synthetic tool that has found application in industry and was awarded the Nobel Prize in Chemistry in 2010. These processes involve the oxidative addition of an organic electrophile to a $Pd(0)$ complex to generate an organopalladium(II) complex, transmetalation by the nucleophilic coupling partner, and reductive elimination to form the carbon-carbon bond and regenerate the $Pd(0)$ complex (**Figure 1.2**).⁴

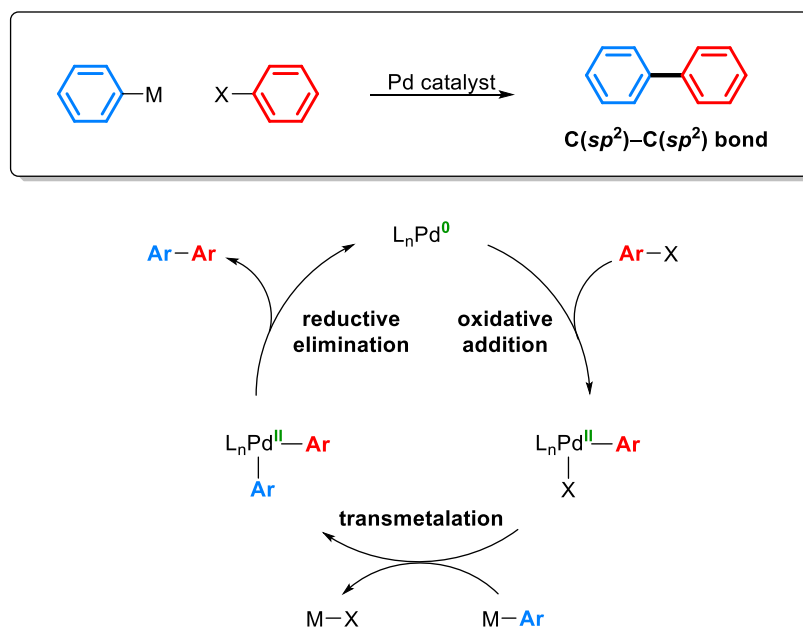
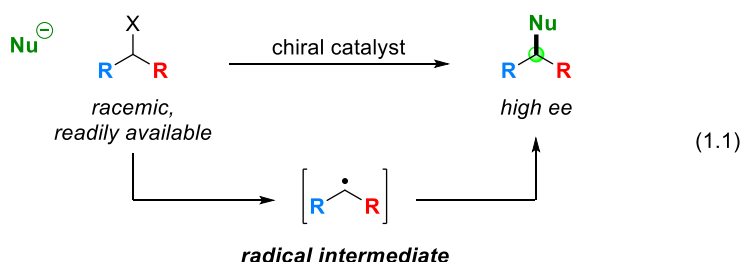


Figure 1.2. Palladium-catalyzed cross-coupling of sp^2 -hybridized substrates.

While methods to form carbon–carbon bonds between sp^2 -hybridized carbons have proven to be remarkably useful tools in organic synthesis, the carbon skeletons of most organic molecules largely consist of bonds between sp^3 -hybridized carbons (“alkyl–alkyl” bonds). Thus, the development of catalysts capable of generating such bonds could open the door to highly efficient syntheses of a broad array of organic molecules. However, in the early 2000s, alkyl electrophiles were considered to be difficult substrates in transition metal-catalyzed nucleophilic substitution reactions,⁵ mainly due to the relatively slow oxidative addition of transition metals toward alkyl halides (especially unactivated 2° and 3° halides) and to the propensity of transition-metal-alkyls to undergo β -hydride elimination.⁶

The net oxidative addition of alkyl halides to transition metals can occur through alternative pathways that do not require direct insertion of the metal into the C–X bond. A two-step oxidative addition is possible, wherein halogen atom abstraction by the transition metal affords an alkyl radical that is subsequently captured by the metal.^{1,7,8} Because this process generates the same metal-alkyl intermediate that would be formed via two-electron oxidative addition, it is possible for metal-catalyzed substitutions of alkyl electrophiles to occur through a pathway analogous to the catalytic cycle illustrated in **Figure 1.2**. This strategy also provides a mechanism for enantioconvergence, as both enantiomers of a racemic alkyl halide are converted to an achiral radical intermediate, which can then converge to one stereoisomer of product through the use of a chiral catalyst (**eq 1.1**).⁹



1.2. Enantioconvergent couplings of alkyl electrophiles catalyzed by nickel

Our group's efforts to apply palladium-based catalysts to alkyl–alkyl couplings led to the finding that these substitution reactions likely proceed through an S_N2 , rather than a radical, pathway for oxidative addition, limiting the scope to 1° alkyl halides.¹⁰ We then began to explore the use of catalysts based on nickel, an earth-abundant metal, to expand the scope of metal-catalyzed cross-coupling reactions to more sterically hindered electrophiles. Compared to palladium, nickel can more readily access a range of oxidation states, giving it a greater propensity to react via a radical pathway.¹¹ Since 2003, the Fu Lab has employed nickel complexes to catalyze couplings between organometallic nucleophiles and 2° and 3° alkyl electrophiles, including a number of enantioconvergent processes.^{1,12} These reactions are believed to proceed via halide abstraction by a nickel(I) complex **A** to generate nickel(II) complex **B** and an alkyl radical (Figure 1.3). Transmetalation of **B** with the organometallic nucleophile yields nickel(II)–alkyl species **C**, which captures the alkyl radical to form nickel(III) complex **D**. Reductive elimination from **D** yields the product and regenerates the active catalyst.^{13,14}

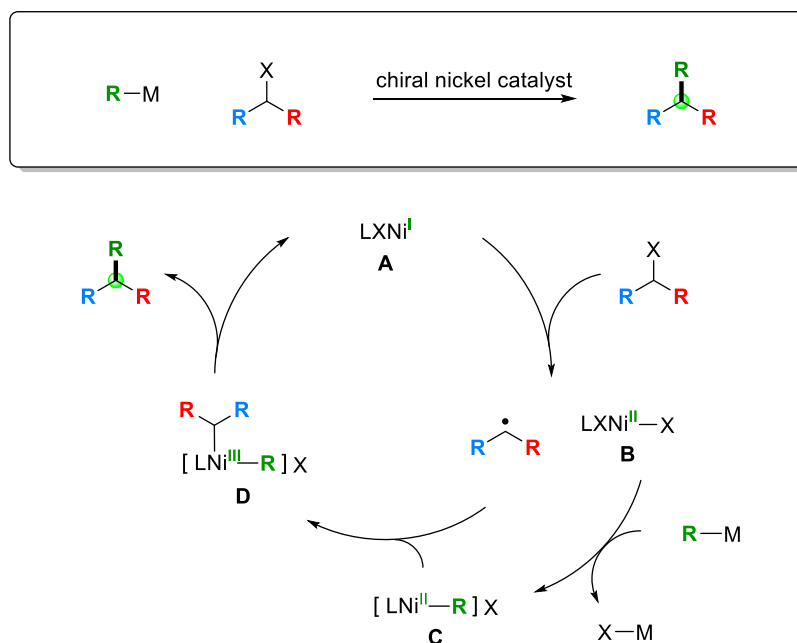


Figure 1.3. Nickel-catalyzed enantioconvergent coupling of an alkyl electrophile via a radical pathway.

We have conducted enantioconvergent substitution reactions of a number of activated and unactivated alkyl electrophiles (top of **Figure 1.4**). In the case of unactivated electrophiles, differentiation between two alkyl groups by the catalyst is possible, although a suitably positioned directing group is usually necessary to obtain good enantioselectivity. Given the versatile reactivity and broad functional group tolerance of these processes, along with the enormous range of conceivable coupling partners, our lab has sought to apply new classes of racemic electrophiles to enantioconvergent, nickel-catalyzed substitution reactions in order to access useful families of compounds that are otherwise difficult to synthesize. Specifically, this thesis will detail our investigations in the asymmetric synthesis of amines (*Chapter 2*), unnatural α -amino acids (*Chapter 3*), and thiols (*Chapter 4*) (bottom of **Figure 1.4**).

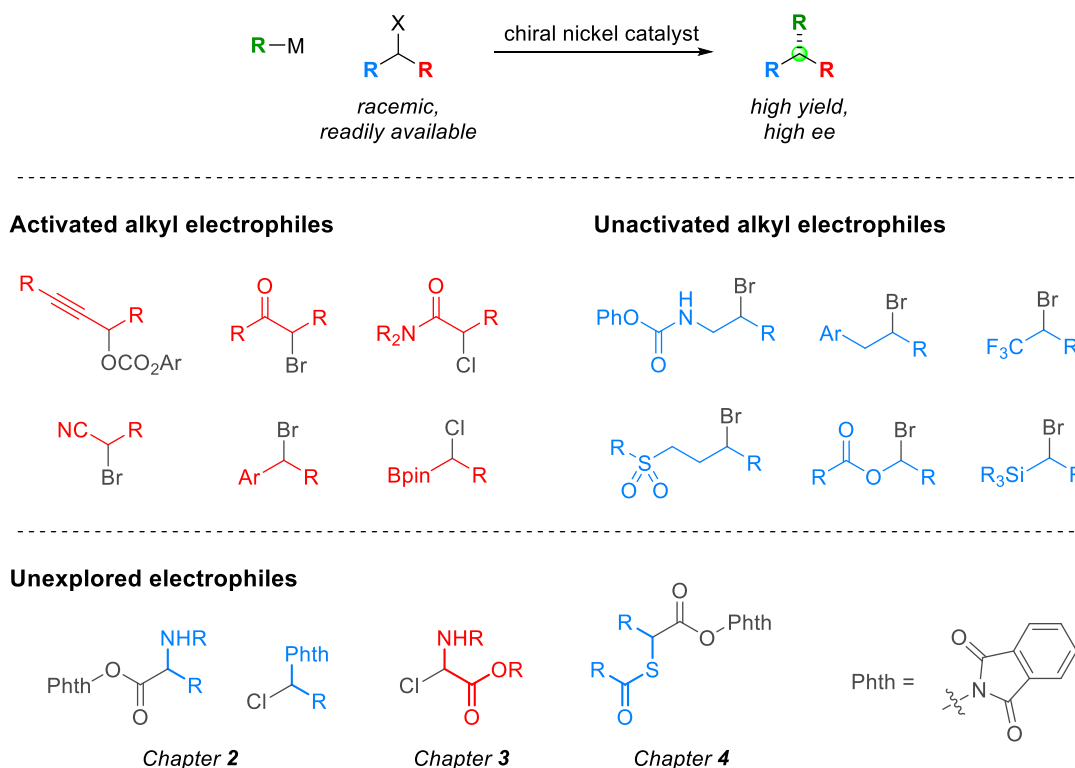


Figure 1.4. Nickel-catalyzed enantioconvergent couplings. Top: examples of activated and unactivated alkyl electrophiles employed previously by our lab. Bottom: unexplored electrophiles that are discussed in this thesis.

While our efforts have primarily focused on carbon-based nucleophiles, nickel can serve as an effective catalyst for substitution reactions of other classes of nucleophiles as well. We have demonstrated that nickel can catalyze couplings of alkyl electrophiles with boron^{15,16} and silicon¹⁷ nucleophiles to access organoboron and organosilicon compounds (**Figure 1.5**). Successfully applying this approach to the formation of C–N, C–O, C–S, and C–F bonds would allow us to readily access other important families of molecules. While our preliminary attempts to apply nickel-based catalysts to couplings by nitrogen, oxygen, and sulfur nucleophiles have been unsuccessful, we have recently discovered that nickel can catalyze the nucleophilic fluorination of unactivated alkyl halides (*Chapter 5*).

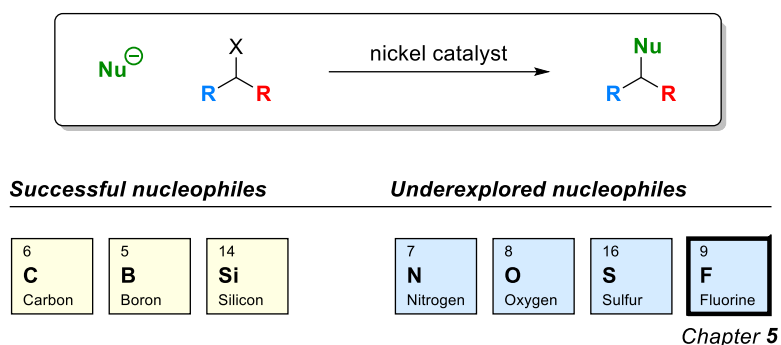
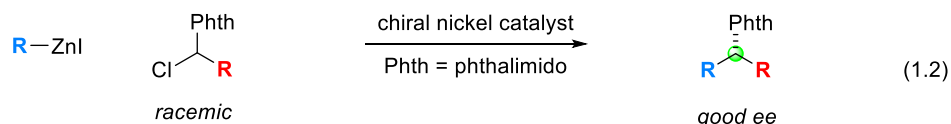


Figure 1.5. Couplings of alkyl electrophiles catalyzed by nickel: successful and underexplored nucleophiles.

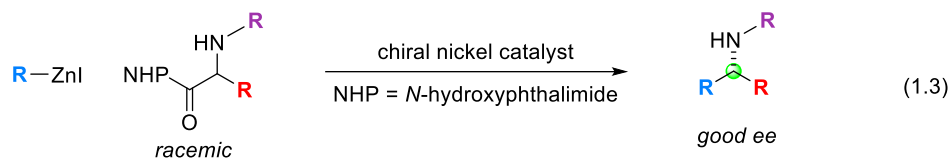
1.3. Overview of individual chapters

This thesis provides an overview of our efforts to apply nickel-catalyzed nucleophilic substitution reactions to the synthesis of diverse families of organic compounds. In **Chapter 2**, we describe two methods for the catalytic enantioconvergent synthesis of amines, which involve the coupling of an alkylzinc reagent with a racemic partner (specifically, an α -phthalimido alkyl chloride and an *N*-hydroxyphthalimide (NHP) ester of a protected α -amino acid) (**eqs 1.2** and **1.3**). For couplings of NHP esters, we further describe a one-pot variant wherein the NHP ester is generated *in situ*, allowing the generation of enantioenriched amines in one step from commercially-available amino acid derivatives (**eq 1.4**); we demonstrate the utility of this one-pot method by applying it to the efficient catalytic enantioselective synthesis of a range of interesting target molecules.

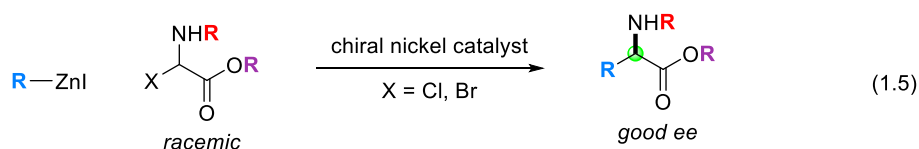
Substitution of alkyl chlorides



Substitution of NHP esters

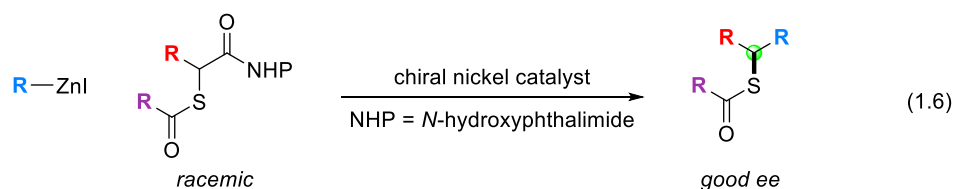


We continued our investigations of racemic electrophiles containing a nitrogen atom geminal to the bond-forming center. In **Chapter 3**, we report the nickel-catalyzed alkylation of racemic α -haloglycine derivatives (a class of electrophile previously unemployed in metal-catalyzed asymmetric cross-coupling reactions) with alkylzinc reagents to generate protected unnatural α -amino acids (**eq 1.5**). This approach is remarkably efficient and facile; the reaction is run under mild conditions, is complete within 30 min, and is tolerant to air and moisture. We apply our method to the generation of several enantioenriched unnatural α -amino acids that have previously been shown to serve as useful intermediates in the synthesis of bioactive compounds.

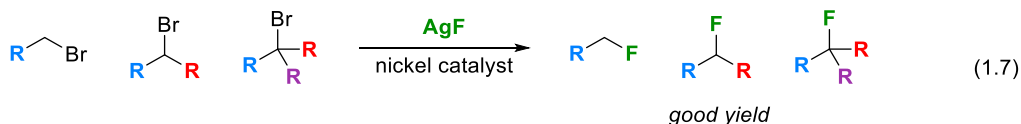


While our group's preliminary attempts to apply sulfur-based nucleophiles to nickel-catalyzed cross-coupling have been unsuccessful, we have remained interested in the synthesis of enantioenriched thiols, which are important synthetic building blocks and frequent constituents of pharmaceuticals. We reasoned that incorporating a sulfur atom into a racemic electrophile and carrying out C–C bond formation would circumvent issues that

could arise during C–S reductive elimination, and we viewed requiring the catalyst to differentiate between an alkyl group and a sulfur substituent as a promising strategy to achieve good enantioselectivity. We detail our approach to target enantioenriched protected thiols in **Chapter 4**. Specifically, we develop a synthesis of NHP esters containing a geminal thioester (a new class of cross-coupling electrophile with no previously reported syntheses) and demonstrate that these NHP esters react with alkylzinc reagents in the presence of a nickel catalyst to form enantioenriched aliphatic thioesters in good ee (**eq 1.6**). We also examine the couplings of other classes of nucleophiles, including alkenyl- and alkynylzinc reagents.



Our lab has been intrigued by the possibility of applying nickel catalysts to couplings of heteroatom nucleophiles. Our investigations of asymmetric nucleophilic fluorinations of racemic alkyl halides revealed that unactivated 1°, 2°, and 3° alkyl halides readily undergo substitution with silver fluoride in high yield when a nickel catalyst is present (**eq 1.7**). In **Chapter 5**, we disclose the surprising discovery of this transformation and explore the effect of electrophile substitution on reactivity. Our method offers a remarkably mild and straightforward approach to nucleophilic fluorination, whose application to unactivated alkyl fluoride synthesis has been impeded by the low nucleophilicity and high basicity of fluoride.



1.4. Notes and references

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