Chapter 1

Emergence of C(sp^3) Ni-Catalyzed Reductive Cross-Couplings:

From Achiral Catalysis to Asymmetric Variants

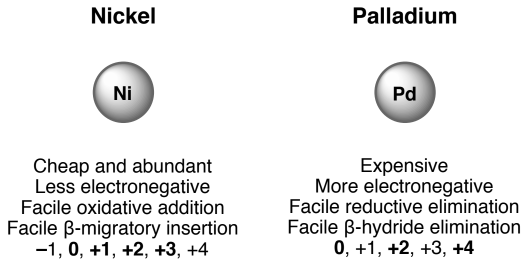
1.1 INTRODUCTION

Metal-catalyzed cross-coupling reactions have become one of the most utilized transformations in medicinal chemistry and in the synthesis of active pharmaceuticals.[1] In addition, these reactions have also found important use in the agrochemical industry and in the production of materials.[2–4] One can contend that the utility behind these methods is due to their simplicity; they allow one to reliably build complex molecules from simple building blocks through straightforward and strategic disconnections. The emergence of this field stemmed from seminal reports in the mid 19th century which describe the use of various metals to produce aryl homocoupling products. However, as reaction development continued and chemists sought ways to promote metal-catalyzed methods in the late 20th century, in particular to favor coupling of distinct partners to form cross-selective products, Pd-catalyzed reactions were more widely developed in contrast to other metals.[5] Research in this newly formed area sought the optimization of conditions to access a wide variety of cross-couplings between nucleophiles and electrophiles, research that continues to be developed even today. In honor of important accomplishments in this area, in 2010 the Nobel Prize was awarded to Heck, Negishi, and Suzuki for their contributions to the development of Pd-catalyzed cross-coupling.

Although these reactions have shown utility in the generation of carbon–carbon and carbon–heteroatom bonds containing C(sp)- and C(sp^2)-hybridized centers, it has been challenging to expand the scope to include C(sp^3)-hybridized centers. Not only are C(sp^3)-hybridized products more difficult to synthesize due to facile β-hydride elimination during Pd-catalyzed cross-couplings, but the generation of C(sp^3)-hybridized centers introduces the opportunity to incorporate chirality into a molecule, and finding appropriate chiral ligands to set stereochemistry with high levels of enantioselectivity is often not trivial.

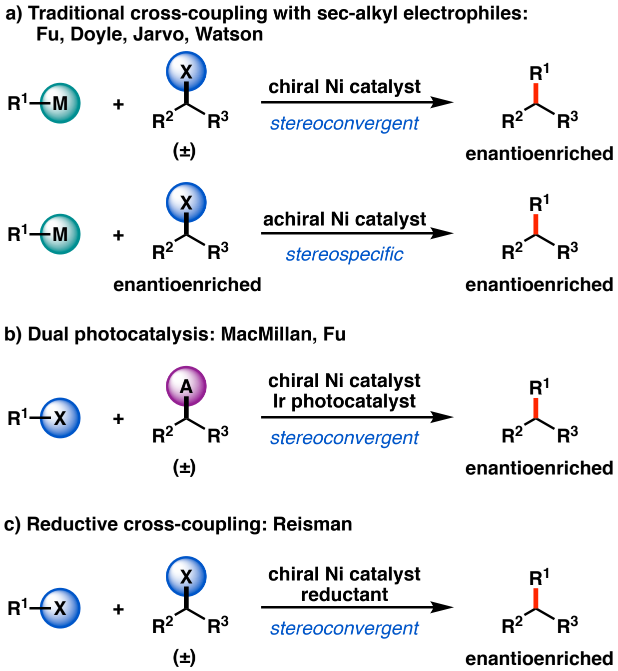
To address these challenges, the development of Ni-catalyzed cross-coupling reactions has garnered interest in the synthesis of molecules containing C(sp^3)-hybridized centers.[6–10] In contrast to Pd, Ni is less electronegative which promotes oxidative addition and mitigates β-hydride elimination; however, it is more challenging for Ni to undergo reductive elimination processes at comparable oxidation states (Figure 1.1). The intrinsic properties of Ni also allow for the access of putative 0, +1, +2, and +3 oxidation states of the metal center during the catalytic cycle, which can permit radical-type oxidative addition processes and enable access to new reaction mechanisms not traditionally seen in Pd catalysis. While these properties promote new modes of reactivity, it is often difficult to harness and control reactive intermediates; therefore, the design of ligands to tune the reactivity of Ni is crucial to the success of reaction methods development.

Figure 1.1 *Properties of Ni and Pd.*



Towards this endeavor, a number of examples of stereoconvergent and stereospecific Ni-catalyzed cross-coupling reactions employing $C(sp^3)$-hybridized electrophiles have been developed (Figure 1.2). Fu and coworkers have reported numerous examples of stereoconvergent cross-couplings to set $C(sp^3)$-hybridized stereocenters through the coupling of racemic alkyl halide electrophiles and a variety of organometallic reagents (e.g., organozinc,[11–22] organoboron,[23–31] organosilicon,[32] organomagnesium,[33] organozirconium[34]) in the presence of a chiral Ni catalyst (Figure 1.2a). Doyle and coworkers expanded these methods to include the cross-coupling of quinolinium and pyridinium ions with organoboron reagents.[35] This stereoconvergent approach allows for the direct synthesis of complex chiral molecules from simple racemic coupling partners and eliminates the need for stoichiometric chiral auxiliaries. Furthermore, Jarvo and Watson have developed stereospecific examples using chiral electrophiles and achiral nickel catalysts, which have also enabled the synthesis of chiral products through stereoinvertive and stereoretentive approaches.[36–46] Despite their utility in cross-couplings reactions, $C(sp^3)$-hybridized organometallic reagents are difficult to prepare in high yield, especially those that are chiral.[47] Overall, these traditional redox-neutral cross-coupling methods require the use of a nucleophile, typically an organometallic reagent, which can suffer from poor stability, air sensitivity, and limited commercial availability.

Figure 1.2 *Ni-catalyzed cross-couplings to form C(sp^3)-hybridized stereocenters.*

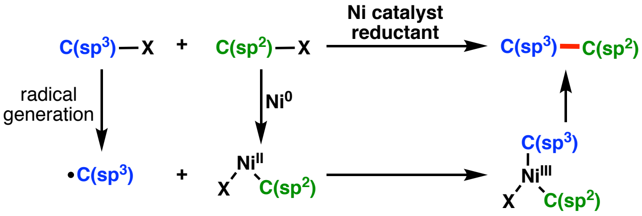


To complement these approaches, reactions that rely on synergistic Ni/photoredox (metallaphotoredox) catalysis[48,49] and Ni-catalyzed reductive cross-electrophile coupling[50–53] have recently been rendered enantioselective (Figure 1.2b–c).[54–60] Most Ni metallaphotoredox methods result from cross-coupling of bench stable carboxylic acids and halide electrophiles;[48,49,55,61–63] however, more recent approaches that generate reactive radical intermediates via C–H abstraction through hydrogen atom transfer (HAT) mechanisms have also been disclosed.[64,65] Typically, these reactions produce either achiral or racemic products; however, a singular example of an asymmetric Ni metallaphotoredox transformation has been developed by MacMillan, Fu, and coworkers (Figure 1.2b).[55]

A number of Ni-catalyzed asymmetric reductive cross-coupling reactions have also been pioneered, which has been the main focus in our laboratory's research surrounding Ni catalysis.[54,56–60] These methods allow inexpensive, bench stable electrophiles as both coupling partners and ultimately proceed with stereoconvergence when appropriate chiral ligands are used (Figure 1.2c). Mild reaction conditions are also employed, allowing methods to exhibit excellent functional group tolerance that would otherwise be incompatible with organometallic reagents. However, one of the major challenges of reductive cross-electrophile couplings, in contrast to conventional redox neutral methods, is the ability to achieve high levels of cross-selectivity. In order to differentiate between the two electrophiles, one can resort to extreme alterations to reagent stoichiometry; however, a more notable approach relies on distinguishing electrophiles via their hybridization which is typically employed by using one C(sp^2)-hybridized electrophile and one C(sp^3)-hybridized electrophile. If differently hybridized electrophiles can selectively react with distinct oxidation states of Ni in the catalytic cycle (e.g. radical type oxidative addition vs. polar mechanism), this could obviate the need for reagent excess and favor cross-selective products instead of homocoupling products.

In considering the mechanism of these transformations, Weix and coworkers have studied the related achiral reductive cross-coupling reaction between aryl iodides and alkyl iodides.[51,66] A few different mechanisms have been postulated and are discussed in greater detail in Chapter 4. A summary of their studies proposed the likelihood of a radical chain mechanism (Figure 1.3). The authors propose that C(sp^3)-hybridized electrophile may result in the formation of an alkyl radical intermediate, which when combined with a Ni(II) complex—resulting from oxidative addition of the C(sp^2)-hybridized electrophile onto Ni(0)—forms a Ni(III) complex. Since reductive elimination from Ni(III) is much more favorable than from Ni(II), the desired cross-coupling product is obtained in good selectivity over the homocoupling products C(sp^2)–C(sp^2) and C(sp^3)–C(sp^3). The application of this reactivity towards method development focuses primarily on the ability to capitalize on the accessible odd oxidation states of Ni to generate and intercept secondary alkyl radicals.

Figure 1.3 *Proposed mechanism for reductive cross-couplings.*



Herein, we discuss the development of Ni-catalyzed reductive cross-coupling reactions using C(sp^3)-hybridized electrophiles is discussed. Initial developments in achiral and racemic systems will be highlighted, and when appropriate, methods that detail developments of asymmetric variants will be discussed. We recognize that electrophiles are defined as electron pair acceptors; however, in the context of cross-coupling this is typically envisioned as an organic halide. As such, a majority of recent efforts in cross-electrophile coupling have been focused in this area. Nevertheless, a number of additional approaches have been developed using "pseudohalides" (i.e., tosylates, mesylates, epoxides, *N*-hydroxyphthalimide esters), which will also be discussed briefly.

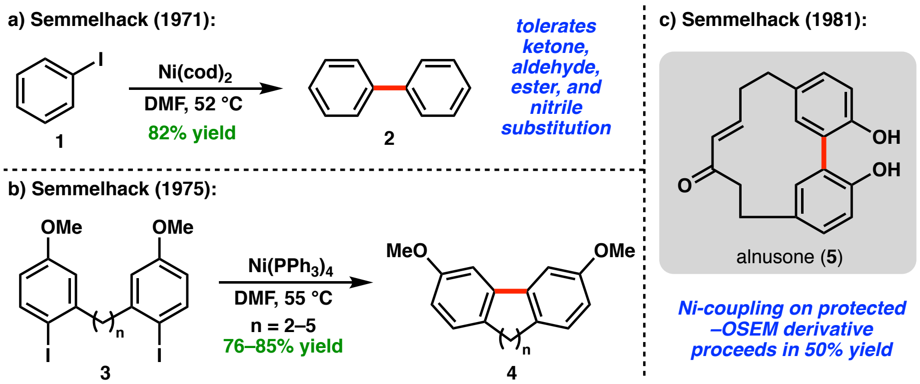
1.2 CROSS-COUPLINGS WITH HALIDE ELECTROPHILES

1.2.1 Initial Developments in C(sp^2) Couplings

Although this review focuses on the use of C(sp^3)-hybridized electrophiles in cross-electrophile coupling, it would be remiss to exclude historical context highlighting initial discoveries regarding Ni-catalyzed reductive homocouplings with C(sp^2)-hybridized electrophiles. These seminal investigations provided the necessary backround that led to the development of this area of research.

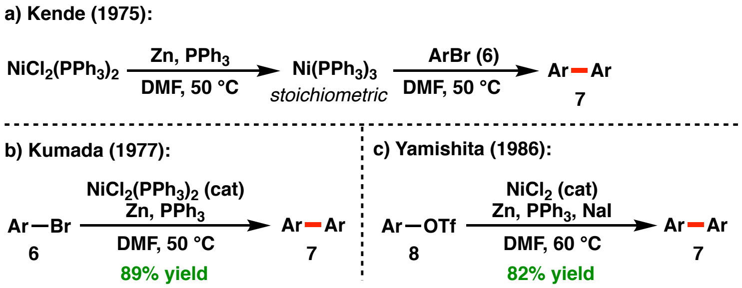
In the early 1970s, Semmelhack and coworkers reported the first homocoupling reactions of aryl iodides (**1**, **3**) in the presence of stoichiometric zerovalent Ni complexes (Figure 1.4).[67,68] These reactions proceeded either intermolecularly with Ni(cod)$_2$ or intramolecularly with Ni(PPh$_3$)$_4$ to afford biaryl products (**2**, **4**) in good yields. Notably, functional groups such as ketones, aldehydes, esters, and nitriles, which would typically interfere with organometallic intermediates, were tolerated in the cross-coupling reaction. In order to highlight its applicability, this method was demonstrated in the total synthesis of a natural product, alnusone (**5**), by a late stage aryl-aryl coupling (Figure 1.4c).[69,70]

Figure 1.4 *Aryl iodide homocoupling with stoichiometric Ni(0).*



Following these initial reports, in 1974 Tolman and coworkers studied the kinetics of ligand dissociation from $Ni(PPh_3)_4$ and discovered that $Ni(PPh_3)_3$ was the active catalyst in the homocoupling transformation.[71] Kende and coworkers then identified a new method for the preparation of *in situ*-generated $Ni(PPh_3)_3$ via a Zn-mediated reduction of $NiCl_2(PPh_3)_2$ in the presence of PPh_3 (Figure 1.4a).[72] This approach alleviated the need for trialkyl- and dialkylalkoxyaluminum reducing agents which necessitate drybox conditions for the preparation of $Ni(PPh_3)_4$. The desired biaryl products (**7**) were then obtained following the treatment of the *in situ* generated, stoichiometric Ni(0) complex with a variety of aryl bromides (**6**). In 1977, Kumada and coworkers reported the first Ni-catalyzed version of the homodimerizaion reaction using a one-pot protocol (Figure 1.4b).[73] Only 2.5 mol % loading of the Ni catalyst was required, as stoichiometric use of Zn was sufficient to reduce the Ni catalyst *in situ* and promote efficient catalytic turnover. Yamishita and coworkers disclosed a similar transformation in 1986, albeit with the use of aryl triflates (**8**), demonstrating that other electrophiles besides halides can undergo reductive homocoupling processes (Figure 1.4c).[74]

Scheme 1.1 *Aryl iodide homocoupling by reduction of Ni(II) with Zn.*



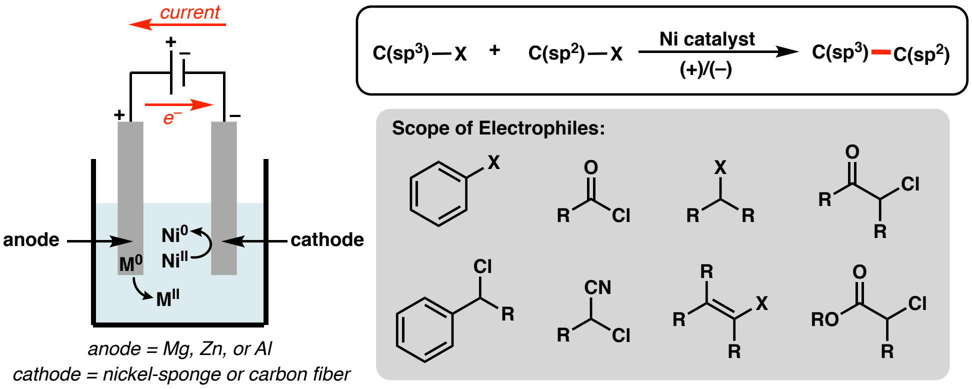
Following seminal studies on reductive homocouplings in the 1970s and 1980s, the 1990s and early 21st century saw the development of Ni-catalyzed cross-coupling methods.

However, due to the necessity to obtain cross-selective products over homocoupling products, the use of redox-neutral transformations between nucleophiles and electrophiles was more widely studied than reductive approaches.

1.2.2 Electrochemical Methods

Initial developments in Ni-catalyzed reductive cross-coupling focused on the use of electrochemical approaches using sacrificial metal anodes as the terminal reductant. A number of cross-electrophile couplings between C(sp^2)- and C(sp^3)-hybridized electrophiles with the use of a single-cell electrochemical setup were developed, most notably by Durandetti and coworkers (Figure 1.5).[75–81] The two electrophiles, an electrolyte, and the requisite Ni catalyst were dissolved in a solvent with high conductivity (e.g. MeCN, DMF), and upon passing current, the desired cross-coupling products were formed. In this setup, reduction processes occurred at the sacrificial metal anode, which dissolves over time as it becomes oxidized to metal cations. Reduction of Ni occurred at the inert cathode, which can then proceed to interact with electrophiles and promote the desired transformation in solution. Although electrochemical approaches were developed

Figure 1.5 *Ni-catalyzed electrochemical cross-electrophile couplings.*



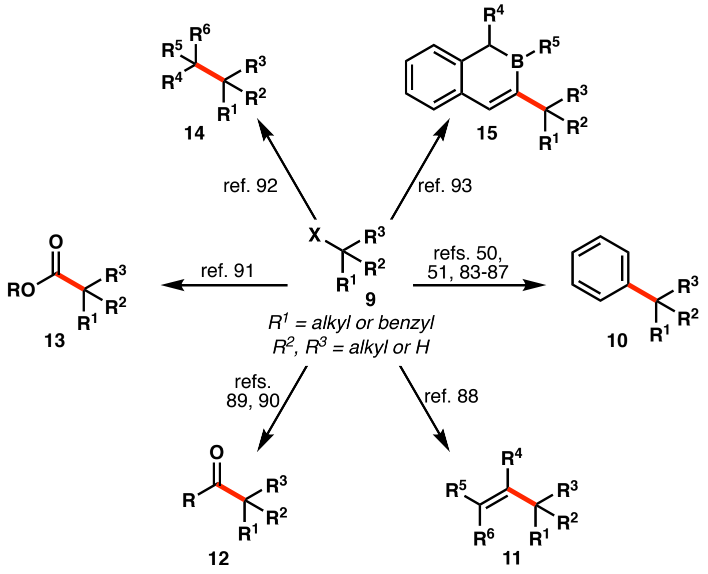
in the mid to late 1990s, the first Ni-catalyzed reductive cross-coupling reaction that used a chemical reductant (i.e. Zn dust) to turn over the catalyst was not reported until 2007.[82]

1.2.3 Heterogeneous Metal Reductants

1.2.3.1 Unactivated Alkyl Electrophiles

An abundant field of research in the development of Ni-catalyzed C(sp^3) cross-coupling has focused on the development of methods that use heterogeneous metal reductants such as Zn and Mn. One particular area concentrated efforts on the use of unactivated alkyl halides (**9**) as one of the coupling partners (Figure 1.6). Weix and coworkers were the first to demonstrate Ni-catalyzed cross-electrophile couplings with unactivated electrophiles,[50,53] and since then a plethora of coupling partners have been extensively investigated, predominantly by the Weix and Gong groups. These reactions form a variety of products (**10**–**15**) when used in cross-coupling reactions in conjunction

Figure 1.6 *Cross-electrophile couplings with unactivated alkyl halides.*

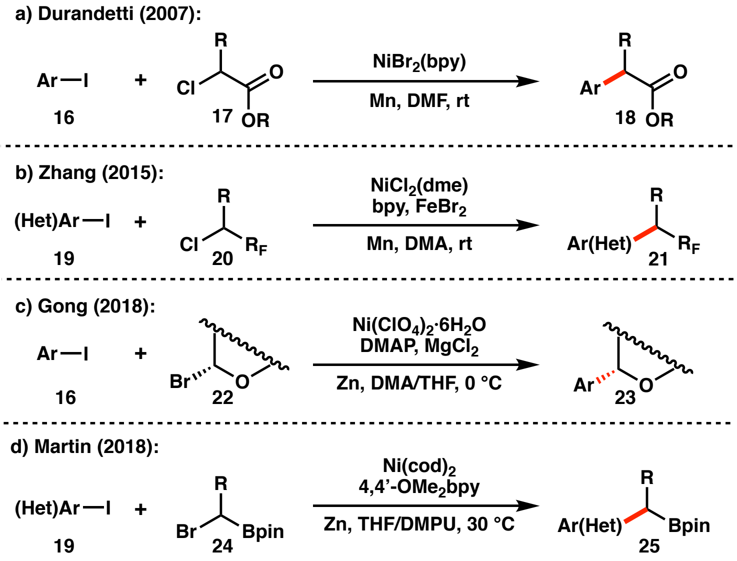


with aryl halides,[50,51,83–87] alkenyl halides,[88] acyl halides,[89,90] chloroformates,[91] alkyl halides,[92] and 3-bromo-azaborines.[93] While most ligands used in these transformations are achiral ligands (e.g. diamine, dtbbpy, phen), Gong and coworkers have demonstrated that PyBOX ligands are effective for alkyl–alkyl couplings,[92] albeit the products are reported as racemic mixtures. Future efforts in the development of asymmetric variants of these coupling reactions is necessary; however, given the unique sets of conditions that are already reported as the C(sp^2)-hybridized electrophile is altered, simply replacing achiral ligands with chiral substitutes is not pragmatic; reactions likely need to be entirely reoptimized to access good yield of analogous chiral products. As asymmetric cross-electrophile couplings all contain activated electrophiles, it is likely that matching the electronics of the catalyst to the lifetime of the alkyl radical is important, which is anticipated to be more challenging with shorter lived alkyl radical species.

1.2.3.2 Activated Alkyl Electrophiles

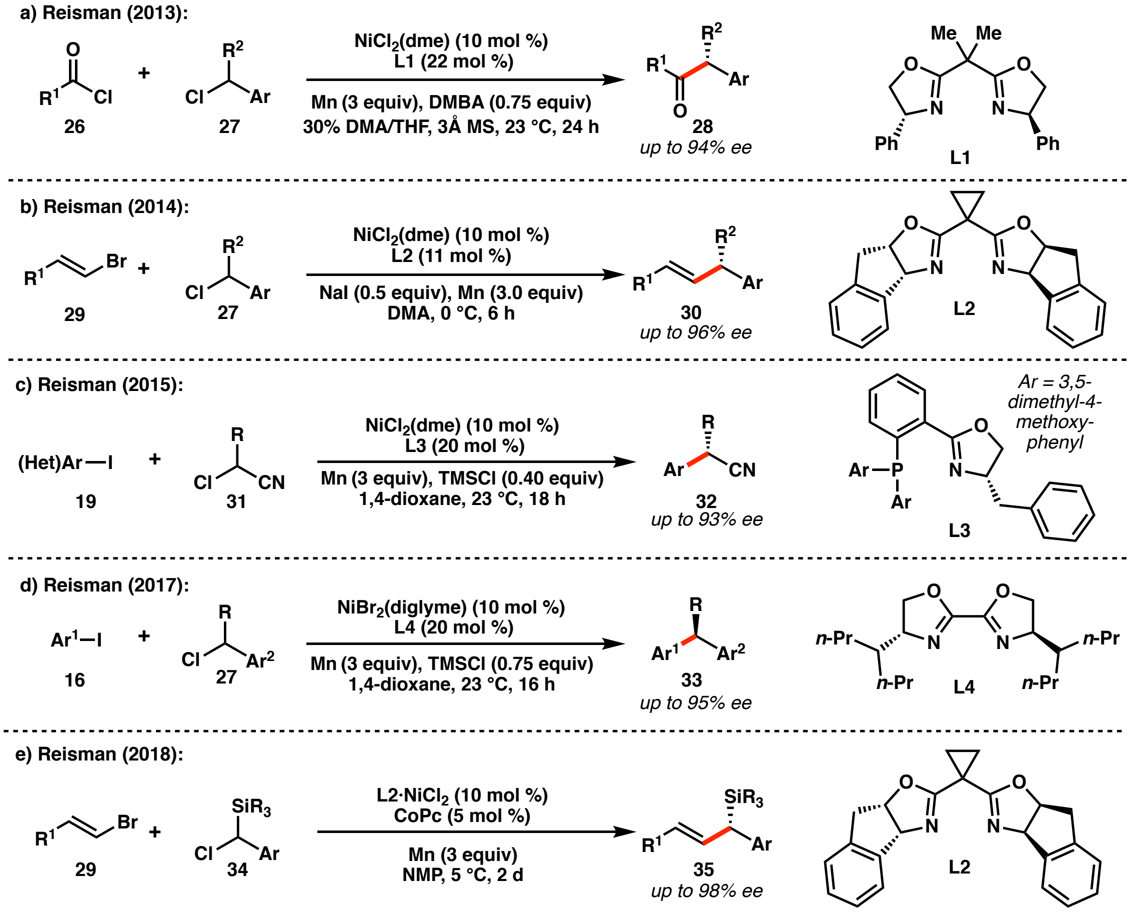
As alkyl radicals are generated on the C(sp^3)-hybridized electrophile following halide abstraction, any substituents present at the α-position will affect the stability and longevity of the generated intermediate. Following investigations using electrochemical methods to conduct cross-electrophile couplings, Durandetti and coworkers were the first to report the use of a chemical reductant (i.e. Mn) to obtain α-arylated ketone products from stabilized alkyl halide electrophiles.[82] Since then, a number of Ni-catalyzed reductive cross-couplings of alkyl halides containing radical stabilizing α-substituents have been developed (Scheme 1.2), including α-groups such as esters,[82] fluorinated alkanes,[94] ethers (glycosides),[95] and pinacol boronates.[96]

Scheme 1.2 *Cross-electrophile couplings with activated alkyl halides.*



Our laboratory has focused on the development of asymmetric Ni-catalyzed cross-electrophile couplings using a broad scope of C(sp^2)-hybridized electrophiles (e.g. aryl iodides (**16**, **19**), alkenyl bromides (**29**), and acid chlorides (**26**)); however, diversifying the C(sp^3)-hybridized electrophile has proven challenging (Scheme 1.3). Thus far, the C(sp^3)-hybridized electrophiles require the use of a radical stabilizing functional group adjacent to the electrophilic carbon, which has afforded success when included as either an aromatic ring (**27**, **32**) or nitrile (**31**) moiety. To obtain high selectivity in the benzylic systems, the use of bis(oxazoline) (BOX) ligands **L1** or **L2**, or bi(oxazoline) (BiOX) ligand **L4**, provides the products in up to 98% enantiomeric excess (ee). With α-chloronitrile electrophiles, an electron-rich BnPHOX ligand **L3** was found to afford the best ee. Although there is some overlap in ligand selection (both alkenylation reactions use the same chiral BOX ligand **L2**), altering the identity of the electrophiles requires extensive screening operations to find the most appropriate ligand and reaction conditions.

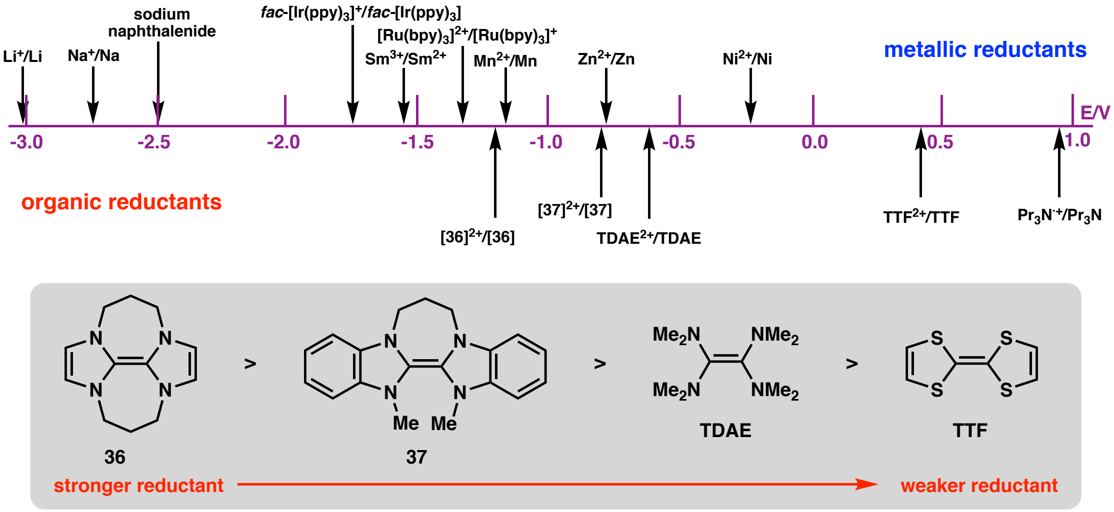
Scheme 1.3 *Asymmetric cross-electrophile couplings with activated alkyl halides.*



1.2.4 Soluble Organic Reductants

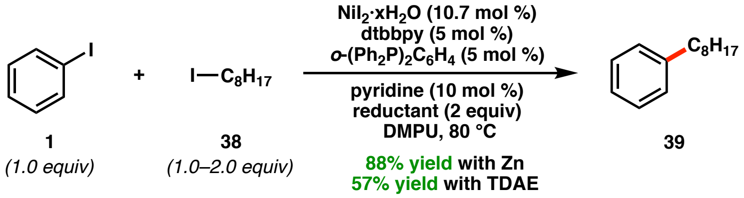
Although most cross-electrophile couplings use either Zn or Mn powder as the stoichiometric reductant, efforts to develop conditions using soluble organic reductants have also been investigated. Since metal reductants render reductive cross-couplings as heterogeneous mixtures, this requires special glassware setups for large scale applications due to capricious stirring effects.[97] While metals and metal complexes display a significant range of reduction potentials, synthetic organic reductants are significantly less reducing (Figure 1.7).[98] However, Murphy and coworkers have demonstrated the synthesis of "super electron donors” **36** and **37**, which have similar reduction potentials to that of Zn and Mn, respectively.[99,100] These stronger organic reductants have yet to be used in cross-electrophile coupling but may find their use in future developments.

Figure 1.7 *Reduction potentials of metallic and organic reductants.*



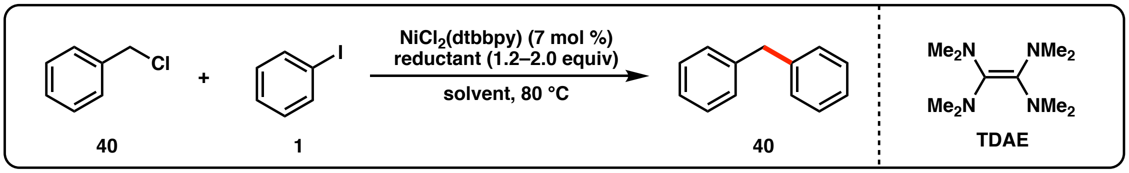
Weix and coworkers were able to demonstrate that tetrakis(*N*,*N*-dimethylamino)ethylene (TDAE) could be used as a soluble reductant in their initial report on the cross-coupling of aryl iodides and alkyl iodides: in comparison to an 88% yield when Mn was used, 57% yield of product **39** was formed with TDAE when 2 equivalents of alkyl iodide **38** was used (Figure 1.8).[50] Further optimization of conditions using benzylic chlorides (**40**) as the alkyl electrophile revealed that only 1.2 equivalents was necessary to promote good yields.[101] One notable advantage over the use of Zn reductants, besides the homogeneity of the reaction and elimination of deleterious side reactivity due to organozinc formation, is the broad applicability of a variety of solvents (Table 1.1). More environmentally friendly solvents such as acetonitrile (MeCN), propylene carbonate

Figure 1.8 *TDAE as a soluble reductant for cross-electrophile couplings.*



(PC), diethyl carbonate (DEC), isopropyl acetate (*i*-PrAc), and 2-methyl-tetrahydrofuran (2-Me-THF), which are widely adopted in the pharmaceutical industry, are effective in this transformation.[102] One drawback, however, is the limited availability for these organic reductants: TDAE is synthesized in three steps, each which possess sensitivity in the products or in reaction workup, and TDAE is still significantly more expensive compared to metal reductants.[59] Methods and detailed procedures to better prepare these reagents are necessary for better adoption in large scale applications.

Table 1.1. *Evaluation of solvents in aryl–benzyl coupling with TDAE.*



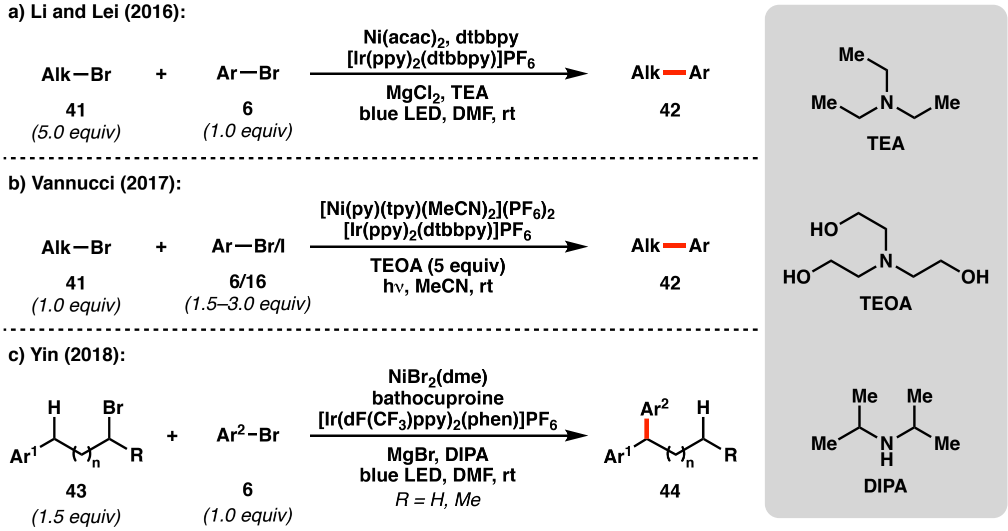
Entry	Solvent	Zn Yield (%)	TDAE yield (%)
1	DMA	82	79
2	MeCN	15	88
3	PC	58	>99
4	DEC	19	75
5	*i*-PrAc	53	79
6	2-Me-THF	51	76
7	PhMe	4	66
8	2-butanol	64	20

1.2.5 Metallaphotoredox Methods

Although most cross-coupling methods that use metallaphotoredox proceed through a redox neutral process, there have been a few seminal reports on reductive cross-couplings of two halide electrophiles.[103] In this approach, stoichiometric metal reductants are replaced with alkyl amines[104–106] or silanols,[107–109] which become oxidized upon single electron transfer from the excited photoredox catalyst. Other metallaphotoredox examples that promote alkyl and aryl halide homocoupling[105,110] as well as alkyl halide carboxylation[111] with CO_2 have also been developed.

The first report of a Ni metallaphotoredox cross-electrophile coupling using an amine as the terminal reductant was reported by Li, Lei, and coworkers in 2016 (Scheme 1.4a).[104] Here, alkyl bromides and aryl bromides were cross-coupled in good yields; however, 5 equivalents of the alkyl bromide was required. This method uses trimethylamine (TEA) to oxidize the excited Ir^{III}* photocatalyst, which in turn reduces Ni in the catalytic cycle. In 2017, Vannucci and coworkers disclosed a similar cross-coupling which proceeds with a terpyridine ligated Ni catalyst and triethanolamine (TEOA) as the terminal reductant (Scheme 1.4b).[105] While an excess of one electrophile is still required, here the aryl halide, the authors found that when the aryl iodide was used, only 1.5

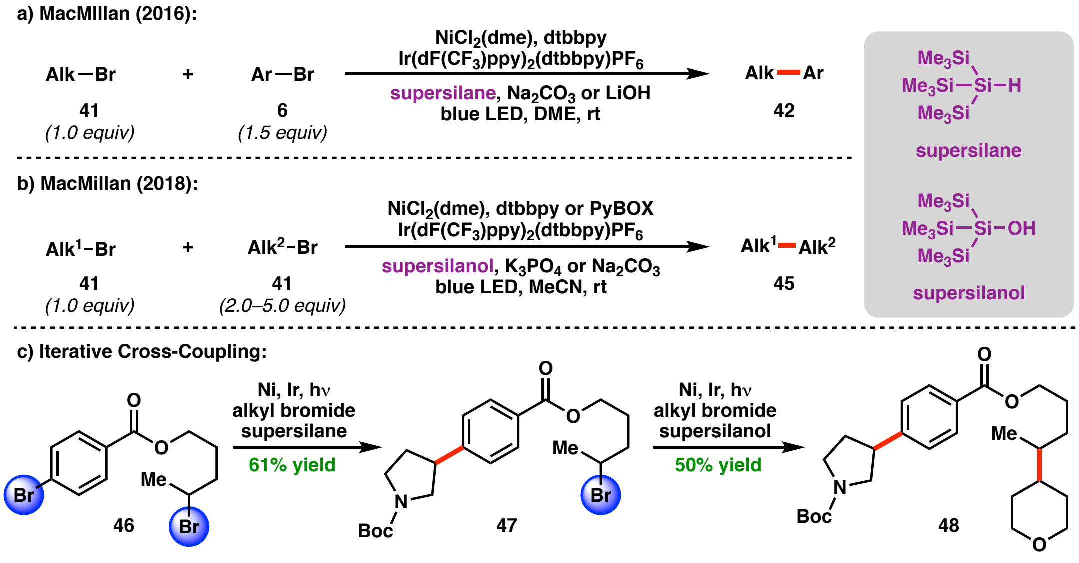
***Scheme 1.4** Metallaphotoredox methods using amine reductants.*



equivalents were necessary to obtain good product yields. Neither of these methods utilized alkyl bromides containing pendant aryl groups. In 2018, Yin and coworkers demonstrated that arylated alkyl bromide electrophiles (**43**) could be employed in metalllaphotoredox cross-coupling when dtbppy was used as a ligand (Scheme 1.4c).[106] When the bathocuproine was used, the 1,1-diarylalkane was instead isolated, indicating that a Ni-catalyzed chain walking mechanism was occurring, likely through iterative β-hydride elimination and subsequent β-migratory insertion. The formation of the branched coupling product is favored over the terminal coupling product due to the stability of the benzylic–Ni complex.

MacMillan and coworkers have well-established that metallaphotoredox catalysis can be used for redox neutral transformations between alkyl, alkenyl, alkynyl, or aryl halides with a plethora of carboxylic acids (and their derivatives). However, they recently expanded their efforts to apply metallaphotoredox to reductive cross-coupling (Scheme

Scheme 1.5 *Metallaphotoredox methods using silane and silanol reductants.*



1.5).[107–109] Key to the reaction development was the identification of tris(trimethysilyl)silane (supersilane) and tris(trimethysilyl)silanol (supersilanol), which were found to be competent terminal reductants. While it is unsurprising that alkyl bromides and aryl iodides can be competent cross-coupling partners (Scheme 1.5a), the latter example depicts alkyl–alkyl couplings that produce high product yields when one electrophile is used in large excess (Scheme 1.5b). Both methods are compatible; an iterative cross-coupling approach demonstrated chemoselectivity for the aryl bromide over the alkyl bromide to form **47** (Scheme 1.5c). Subsequent alkylation afforded the bisfunctionalized product **48**.

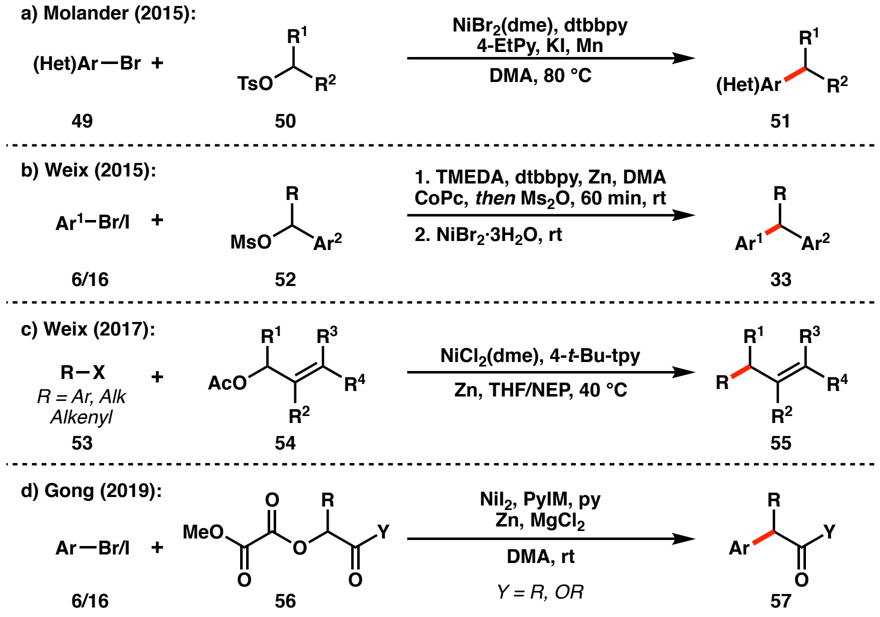
While these transformations use achiral catalysts and provide racemic products, preliminary results using an achiral PyBOX ligand were reported. We envision that in time, asymmetric variants of metallophotoredox reductive cross-couplings will be developed and utilized in a variety of synthetic contexts.

1.3 CROSS-COUPLINGS WITH PSEUDOHALIDE ELECTROPHILES

1.3.1 Oxygen Electrophiles

Although organohalides represent the most broadly used and widely developed class of electrophiles employed in Ni-catalyzed reductive cross-couplings, other pseudohalides have also been utilized. One particular type is the use of oxygen-based electrophiles derived from alcohols, such as alkyl mesylates[60,112], alkyl tosylates[113], allylic acetates[86,114–117], and alkyl oxalates[118,119] (Scheme 1.6). Although recent reports have investigated the use of Lewis acid catalysis to activate allylic alcohols towards oxidative addition,[120] typically activating groups are required for C–O bond insertion. As activated oxygen-based electrophiles are generally less reactive than their halide counterparts, the addition of co-catalysts to aid in radical generation processes has been used by Weix and coworkers (Scheme 1.6b).

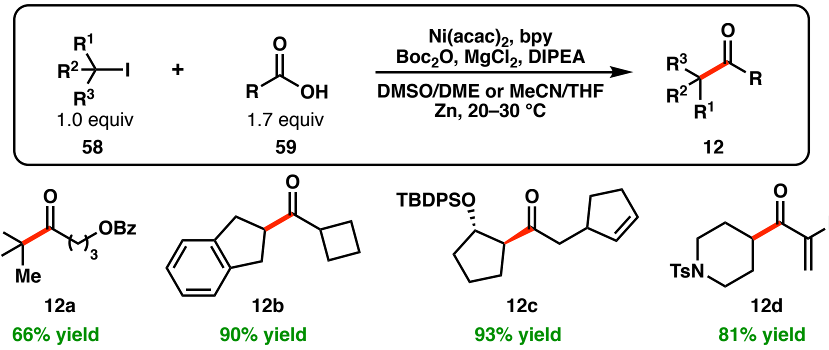
Scheme 1.6 *Selected examples of reactions using oxygen-based electrophiles.*



1.3.2 Carboxylic Acid Derivatives

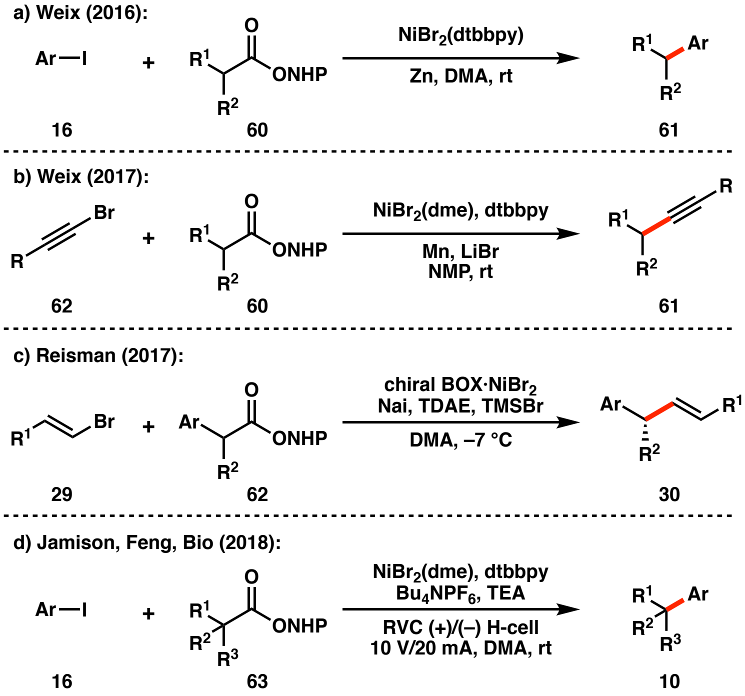
The first cross-electrophile couplings using carboxylic acid derivatives (i.e. anhydrides) utilized these electrophiles as C(sp^2) coupling partners. As a follow-up to previous work,[121] Gong and coworkers were able to prepare unsymmetrical ketones via the cross-coupling of alkyl iodides (**58**) and alkyl carboxylic acids (**59**) in the presence of Boc$_2$O, which facilitates *in situ* anhydride formation, thus making the acid electrophile more prone to oxidative addition into the C–O bond (Figure 1.9).[122] Similar studies have been conducted by Liao and coworkers using symmetrical anhydrides and aryl iodides.[123]

Figure 1.9 *Synthesis of ketones from carboxylic acid derivatives.*



The use of alkyl carboxylic acids as C(sp^3) cross-coupling partners was ultimately envisioned via the formation of redox active ester derivatives such as *N*-hydroxyphthalimide (NHP) esters (Scheme 1.7). In 1988, Okada and Oda first demonstrated that the reduction of the phthalimide moiety induced decarboxylation to form alkyl radical species which could be intercepted by Michael acceptors.[124,125] More recently,

Scheme 1.7 *NHP esters derived from carboxylic acids as C(sp^3) electrophiles.*

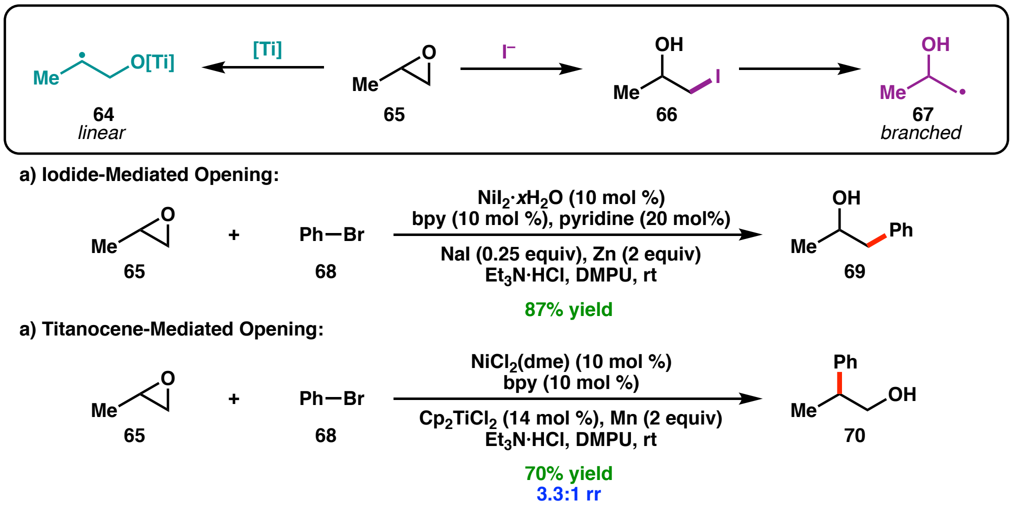


NHP esters have been utilized in Ni-catalyzed cross-electrophile couplings as alkyl radical precursors for arylation,[126,127] alkenylation,[59] and alkynylation reactions.[128] The first report of an enantioselective cross-coupling using NHP esters was demonstrated by Reisman and coworkers using a chiral BOX ligand.[59]

1.3.3 Epoxides and Aziridines

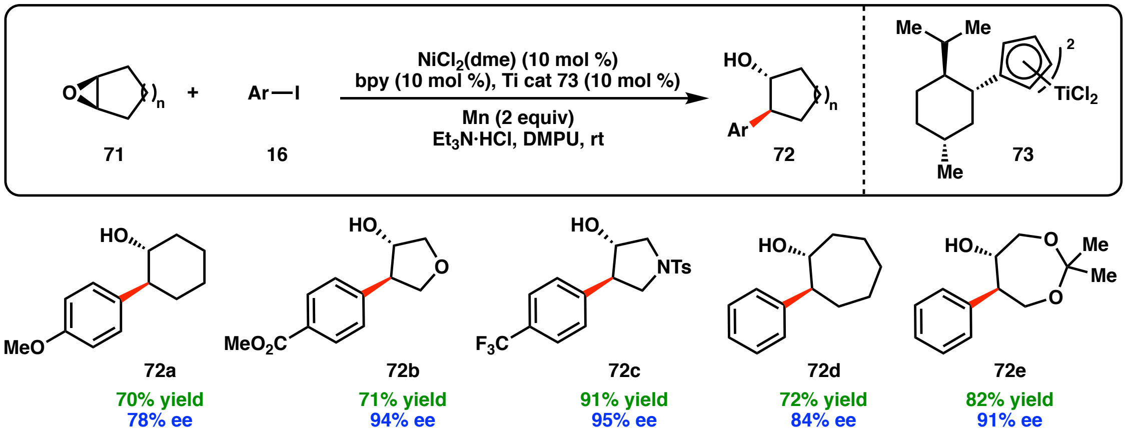
Ring opening reactions of epoxides and aziridines can provide an additional source of C(sp^3) alkyl radicals. Weix and coworkers demonstrated that epoxides (65) can be used in regiodivergent reductive cross-couplings to form either the branched or the linear coupling products depending on the mode of epoxide activation (Figure 1.10). Addition of NaI can lead to the formation of the branched alkyl radical (**67**) via the iodohydrin (**66**); in contrast, activation and ring-opening of the epoxide by titanocene complexes can result in the linear alkyl radical (**64**). This strategy was demonstrated in the Ni-catalyzed arylation of **65**, wherein iodide-mediated ring-opening afforded arylated product **69** and titanocene-mediated ring-opening afforded **70** as a 3.3:1 regiomeric ratio of isomers.[129]

Figure 1.10 *Ni-catalyzed cross-electrophile arylation of epoxides.*



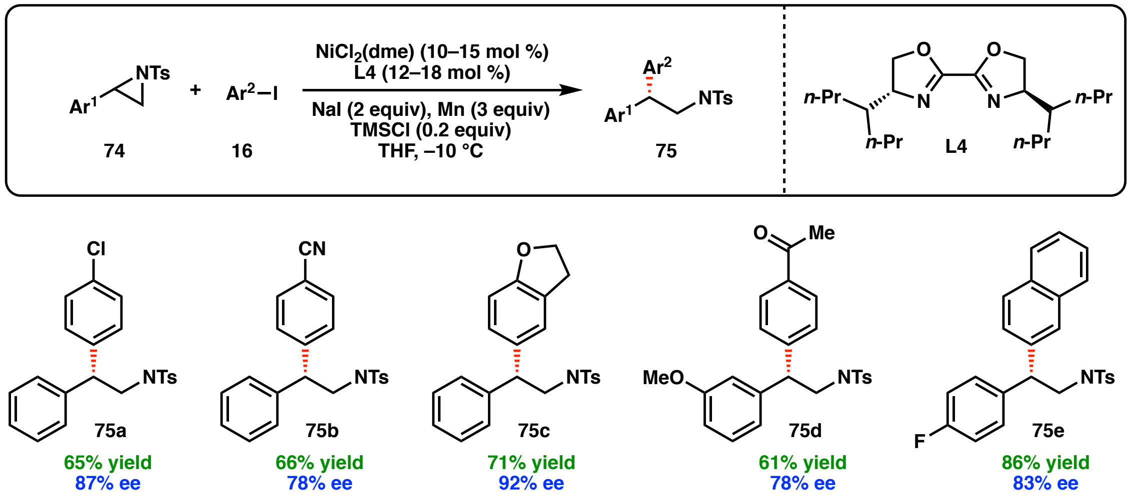
Following this study, Weix and coworkers showed that chiral titanocene complexes could be used to form enantioenriched products from *meso*-epoxides via a desymmeterization strategy (Figure 1.11).[130] The use of chiral titanocene catalyst **73** derived from (–)-menthone in the was able to provide arylated products following interception of the alkyl radical with the Ni catalyst. This method was applied towards 5-, 6-, and 7-membered cyclic epoxides to form the products (**72a**–**e**) in good yield with generally high levels of enantioselectivity.

Figure 1.11 *Enantioselective arylation of meso-epoxides.*



Doyle and coworkers recently reported an asymmetric Ni-catalyzed cross-coupling of styrenyl aziridines (**74**) with aryl iodides (**16**) using NiCl$_2$(dme) and BIOX ligand **L4**.[131] The diaryl alkane products (**75**) formed in this reaction provided the highest ee when a BIOX ligand containing 4-heptyl groups was used, although some products still suffered from lower ee due to arene substitution. Interestingly, **L4** is the same ligand developed in the Reisman group for the cross-coupling of benzyl chlorides and aryl iodides to form the same diaryl alkane products.[54] In collaboration with the Sigman laboratory, multivariate analysis using computationally-derived parameters of a series of BIOX ligands was investigated. The obtained model depicts strong correlations between the predicted and measured $\Delta\Delta G^{\ddagger}$ when the ligand width, charge on the oxazoline N, and ligand polarizability are included. Interpretations suggest a long alkyl chain is best predicted. This study highlights the first approach at using ligand parameterization to provide rationale into observed enantioselectivity in asymmetric Ni-catalyzed reductive cross-couplings. We predict these types of studies can not only help explain the reaction mechanism, but also may be used to predict more selective ligands in the future.

Figure 1.12 *Enantioselective arylation of styrenyl aziridines.*



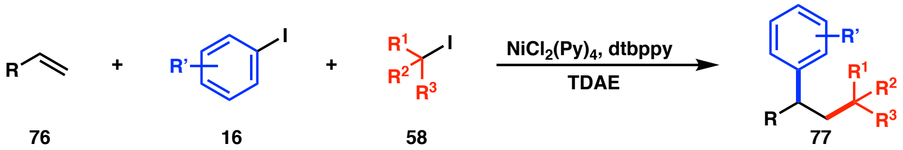
1.4 SYNTHETIC APPLICATIONS

A number of Ni-catalyzed cross-electrophile couplings between $C(sp^2)$–$C(sp^3)$ and $C(sp^3)$–$C(sp^3)$ centers have been developed. While advances in this methodology continue in both achiral and asymmetric regimes, other applications have recently emerged which include alkene functionalization and utility in the synthesis of natural products.

1.4.1 Alkene Functionalization

Recent developments have examined three-component couplings that incorporate an intermediate radical acceptor, thus joining together three fragments during the cross-electrophile coupling. Nevado and coworkers found that the use of $NiCl_2(Py)_4$ and dtbppy could successfully catalyze the dicarbofunctionalization reaction between terminal alkenes (**76**), aryl iodides (**16**), and alkyl iodides (**77**) with the use of TDAE as the terminal reductant (Scheme 1.8).[132] While the alkene scope is limited to Michael acceptors or activated allylic systems, this represents the first reductive variant of Ni-catalyzed dicarbofunctionalization. We envision that future advances in the field of Ni-catalyzed cross-electrophile couplings will continue efforts to intercept feedstock alkenes. Peng and coworkers have successfully demonstrated an intramolecular variant using an unactivated alkene system.[133] Tuning the electronic parameters of the catalyst will likely play an important role in tuning the lifetime of the alkyl radical.

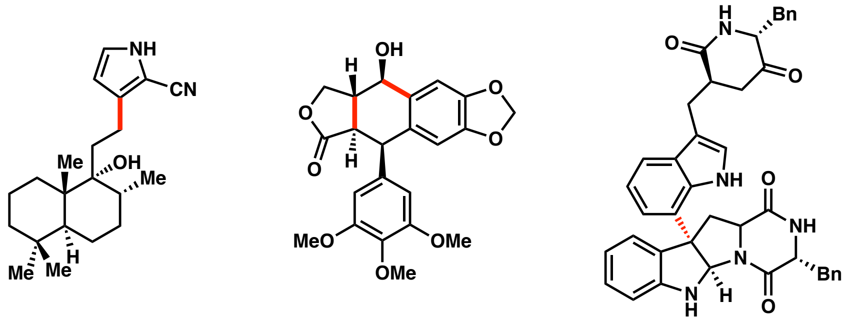
***Scheme 1.8** Reductive dicarbofunctionalization of alkenes.*



1.4.2 Natural Product Synthesis

Ni-catalyzed reductive cross-couplings have also found recent use in the synthesis of various natural products, including vitepyrroloid A (**78**),[134] podophyllotoxin (**79**),[135] and asperazine (**80**)[136] (Figure 1.13). These methods highlight the use of aryl–alkyl couplings and carbodifunctionalization strategies to access the natural products via key bond disconnections. While asymmetric variants of cross-electrophile couplings have yet to be applied in natural product synthesis, we envision the continued development of new asymmetric methods will ultimately find its use in this synthetic context.

Figure 1.13 *Natural products synthesized via cross-electrophile couplings.*



vitepyrroloid A **(78)** podophyllotoxin **(79)** asperazine **(80)**

1.5 CONCLUSION

In summary, Ni-catalyzed reductive cross-electrophile couplings using C(sp^3)-hybridized electrophiles is a diverse area of research with various applications in organic chemistry. These methods utilize a Ni catalyst to cross-couple bench-stable electrophiles in the presence of a terminal reductant. The ability to access alkyl radical intermediates allows for stereoconvergence to form enantioenriched products when chiral ligands are used, further expanding the utility of these transformations. The surge of new methods in this field has seen rapid development within the past decade and is likely to see numerous new modes of reactivity emerge in the years to come.

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