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Enantioselective C(sp^2)–C(sp^3) Bond Construction by Ni Catalysis

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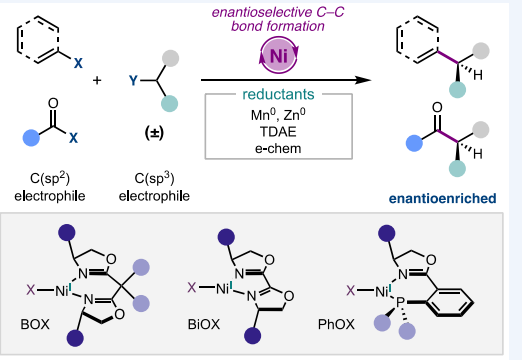
CONSPECTUS: After decades of palladium dominating the realm of transition-metal-catalyzed cross-coupling, recent years have witnessed exciting advances in the development of new nickel-catalyzed cross-coupling reactions to form C(sp^3) centers. Nickel possesses distinct properties compared with palladium, such as facile single-electron transfer to C(sp^3) electrophiles and rapid C–C reductive elimination from Ni^{III}. These properties, among others, make nickel particularly well-suited for reductive cross-coupling (RCC) in which two electrophiles are coupled and an exogenous reductant is used to turn over the metal catalyst. Ni-catalyzed RCCs use readily available and stable electrophiles as starting materials and exhibit good functional group tolerance, which makes them appealing for applications in the synthesis of complex molecules. Building upon the foundational work in Ni-catalyzed RCCs by the groups of Kumada, Durandetti, Weix, and others, as well as the advancements in Ni-catalyzed enantioselective redox-neutral cross-couplings led by Fu and co-workers, we initiated a program to explore the feasibility of developing highly enantioselective Ni-catalyzed RCCs. Our research has also been driven by a keen interest in unraveling the factors contributing to enantioinduction and electrophile activation as we seek new avenues for advancing our understanding and further developing these reactions.



In the first part of this Account, we organize our reported methods on the basis of the identity of the C(sp^3) electrophiles, including benzylic chlorides, *N*-hydroxyphthalimide (NHP) esters, and α-chloro esters and nitriles. We highlight how the selection of specific chiral ligands plays a pivotal role in achieving high cross-selectivity and enantioselectivity. In addition, we show that reduction can be accomplished not only with heterogeneous reductants, such as Mn^0, but also with the soluble organic reductant tetrakis(dimethylamino)ethylene (TDAE), as well as electrochemically. The use of homogeneous reductants, such as TDAE, is well suited for studying the mechanism of the transformation. Although this Account primarily focuses on RCCs, we also highlight our work using trifluoroborate (BF_3K) salts as radical precursors for enantioselective dual-Ni/photoredox systems.

At the end of this Account, we summarize the relevant mechanistic studies of two closely related asymmetric reductive alkenylation reactions developed in our laboratory and provide a context between our work and related mechanistic studies by others. We discuss how the ligand properties influence the rates and mechanisms of electrophile activation and how understanding the mode of C(sp^3) radical generation can be used to optimize the yield of an RCC. Our research endeavors to offer insights on the intricate mechanisms at play in asymmetric Ni-catalyzed RCCs with the goal of using the rate of electrophile activation to improve the substrate scope of enantioselective RCCs. We anticipate that the insights we share in this Account can provide guidance for the development of new methods in this field.

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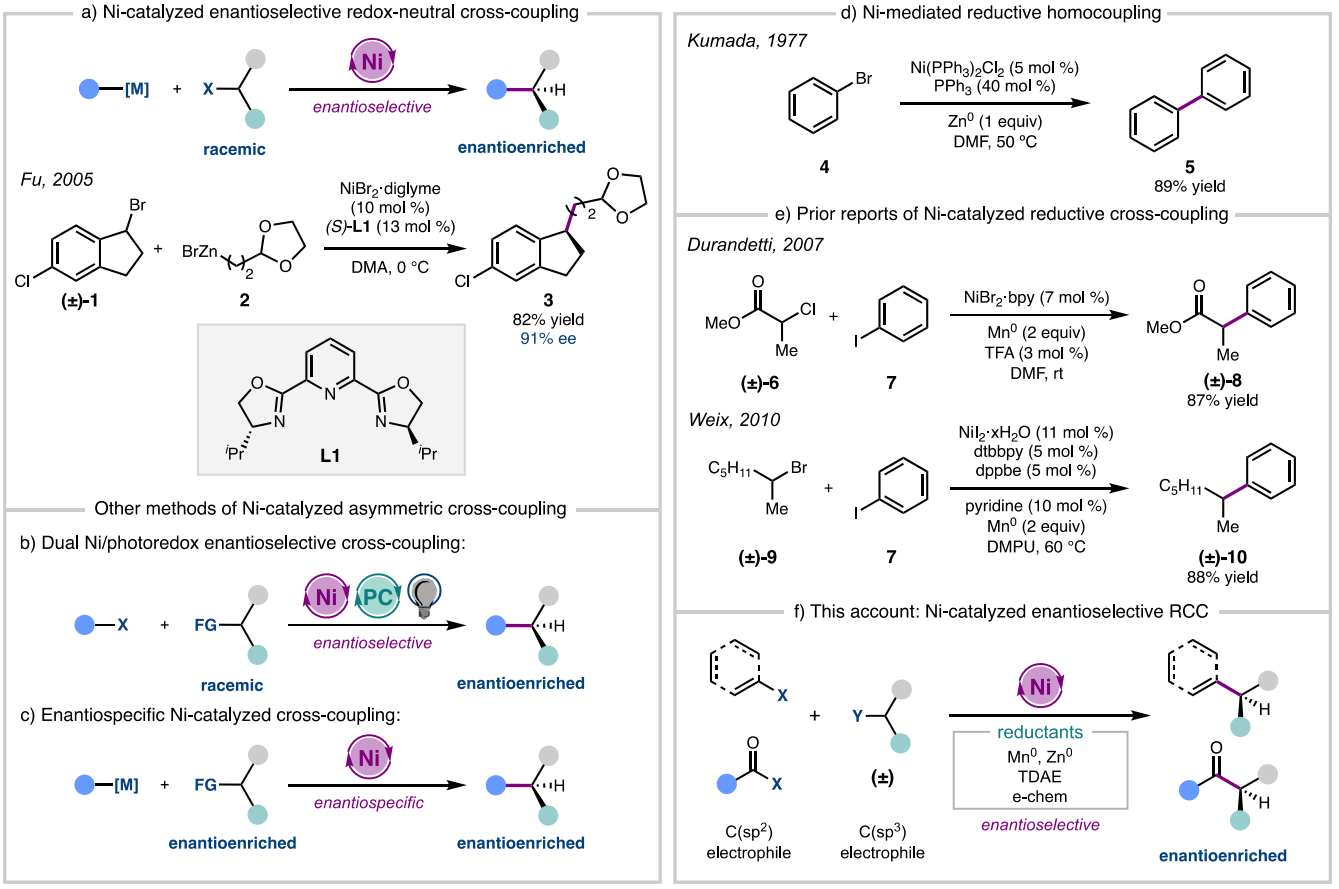

Figure 1. Seminal reports and schematic representations of (a) Ni-catalyzed enantioselective cross-coupling, (b) dual-Ni/metallaphotoredox for asymmetric cross-coupling, (c) Ni-catalyzed enantiospecific cross-coupling, (d) Ni-mediated reductive homocoupling, (e) Ni-catalyzed RCCs, and (f) Ni-catalyzed enantioselective RCCs.

coupling to prepare diarylalkanes, which necessitated the development of the 4-heptyl-BiOX ligand.

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2. INTRODUCTION

The development of enantioselective reactions is a challenging but important discipline within organic chemistry with applications in natural product synthesis, drug development, and materials science. Amidst the array of methods to generate stereogenic centers through C−C bond formation, transition-metal-catalyzed cross-coupling has emerged as a powerful tool. Whereas early efforts to develop redox-neutral palladium-catalyzed cross-coupling reactions of either C(sp^3) nucleophiles or electrophiles were plagued by challenges, such as slow transmetalation and β-hydride elimination, nickel has emerged as a versatile metal to catalyze C(sp^3) bond formation.[5] Nickel, compared with palladium, offers distinct reactivity that is advantageous for constructing C(sp^3) centers, including facile oxidative addition ($Ni^{0/II}$, E_0 = −0.26 V vs SHE versus $Pd^{0/II}$, E_0 = 0.95 V vs SHE), slower β-hydride elimination, and a range of accessible oxidation states ($Ni^{0/I/II/III/IV}$) that enable diverse modes of electrophile activation.[6] In pioneering studies, Fu and co-workers reported the first examples of Ni-catalyzed enantioconvergent cross-couplings in 2005 in which racemic secondary alkyl halides could be coupled with aryl zinc nucleophiles with high enantioselectivity (Figure 1a).[5,7−9] Since these initial reports, complementary strategies, such as enantioselective dual-Ni/photoredox catalysis (Figure 1b)[10] and enantiospecific Ni-catalyzed transformations (Figure 1c)[11,12] have been developed to stereoselectively cross-couple C(sp^3) partners. Many of these transformations are redox-neutral as they involve the use of both an electrophilic and a nucleophilic fragment without a net change in the oxidation state of the reaction partners.

In addition to redox-neutral cross-coupling, Ni has emerged as a particularly good catalyst for reductive cross-coupling (RCC) in which two electrophilic fragments are coupled, and an exogenous reductant is used to turn over the catalyst.[13−15] The ability to replace organometallic nucleophiles with electrophiles is advantageous, since they are generally more commercially available, are stable, and exhibit greater func-

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tional group tolerance compared with their organometallic counterparts.

Although there has been a resurgence in interest in Ni-catalyzed RCCs over the past decade, these reactions were first reported in the 1970s. Following initial reports of stoichiometric Ni-mediated reactions of allylic[16] and aryl halides,[17,18] in 1977, Kumada and co-workers described the Ni-catalyzed homodimerization reaction of aryl bromides where Zn^0 powder was used to generate the active catalyst *in situ* and promote turnover (Figure 1d).[19] Nevertheless, because of the challenges associated with achieving cross-selectivity between distinct aryl electrophiles, the use of redox-neutral cross-couplings has remained the prevalent focus of research for several decades. Following initial development of electroreductive Ni-catalyzed cross-couplings between α-chloroesters and aryl bromides,[20,21] in 2007, Durandetti and co-workers demonstrated that Mn^0 could be used as the chemical reductant to synthesize α-aryl esters (e.g., **8**, Figure 1e).[22] In 2010, Weix and co-workers reported the first Ni-catalyzed RCC of unactivated C(sp^3) electrophiles (e.g., **9**) with aryl iodides, also by utilizing Mn^0 as the stoichiometric chemical reductant (Figure 1e).[23] In the decade since, research on Ni-catalyzed RCC has flourished, thereby expanding its scope to include a plethora of activated and unactivated C(sp^3) electrophiles.

In 2011, our laboratory initiated a program focused on the development of Ni-catalyzed, enantioselective reductive cross-coupling (RCC) reactions.[1] Although the detailed mechanisms of RCC reactions are complex and were poorly understood when we began our studies, we recognized that activation of the C(sp^3) electrophile likely proceeded through radical intermediates, in analogy to many of the redox-neutral Ni-catalyzed cross-couplings developed by Fu and others.[24] As a result, we became interested in the possibility of using chiral Ni complexes to cross-couple *sec*-alkyl electrophiles by stereoconvergent processes (Figure 1f). Indeed, our initial foray into Ni catalysis was driven by a challenge encountered in our total synthesis program, which required an enantioselective synthesis of an α,α-disubstituted carbonyl compound (vide infra). We were drawn to acyl cross-coupling as an alternative to auxiliary-based enolate alkylation methods.[25,26] Moreover, we anticipated that the functional group compatibility of these reactions would make them well-suited for downstream applications in total synthesis.

In this Account, we provide an overview of our work in Ni-catalyzed enantioselective cross-coupling. The discussion will be organized according to the identity of the C(sp^3) coupling partner and will close with a discussion of mechanism.

3. SYNTHETIC METHOD DEVELOPMENT

3.1. Benzylic Chlorides as C(sp^3) Electrophiles

Our interest in Ni-catalyzed enantioselective RCC methods was inspired by a challenge encountered during the synthesis of the natural product maoecrystal Z,[27] where we required an enantiopure alkyl iodide building block (**11**, Figure 2). Although we ultimately resorted to a chiral auxiliary approach, our brainstorming during this project prompted us to investigate catalytic alternatives that obviate the use of a stoichiometric stereocontrol element and cryogenic reaction temperatures.

Motivated by this synthetic challenge, we began investigating the Ni-catalyzed reductive cross-coupling between acyl

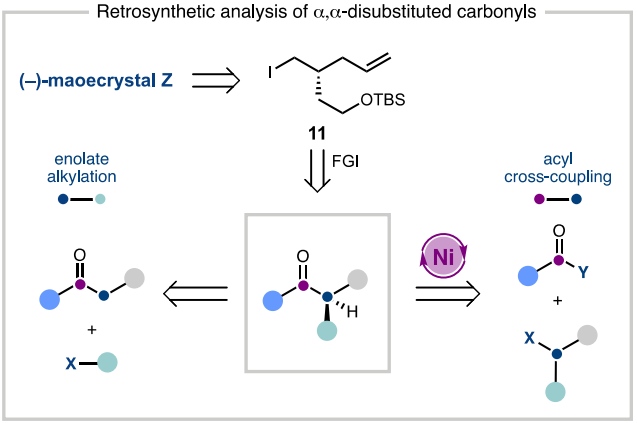

Figure 2. Schematic representation of initial thought process for methodology development.

chloride **12** and benzylic chloride **13** using chiral nitrogen-based ligands.[1] Preliminary studies identified that the phenyl-substituted bis(oxazoline) (BOX) ligand **L2** provided promising enantioselectivity, although the yield of α-phenylketone **14a** was very low (Figure 3).[1] Extensive investigations of reaction parameters revealed that a mixed tetrahydrofuran (THF)−dimethylacetamide (DMA) solvent system delivered the optimal balance between the reactivity and enantioselectivity. Furthermore, the addition of dimethylbenzoic acid (DMBA) proved to be crucial for suppressing undesired homocoupling of the benzylic electrophiles. Under the final conditions, acyl chloride **12** and benzylic chloride **13** could be cross-coupled to give enantioenriched ketone **14a** in 85% yield and 92% ee. Several aspects of this transformation are noteworthy. (1) The mild conditions avoid racemization of the α-arylketone products, which is a challenge faced in other transition-metal-mediated arylation reactions that employ strong base or high temperatures. (2) The reaction tolerates functional groups like primary alkyl halides (**14h** and **14i**) and can provide β-siloxy ketone products (**14e**), which would be prone to elimination under strongly basic conditions. (3) This catalyst-controlled method can provide diastereoselective access to products with remote stereocenters, as observed in the coupling of a β-stereogenic acid chloride to give either diastereomer of **14j** with high diastereomeric ratio (dr).

Although our initial interest in Ni-catalyzed asymmetric RCC derived from the need to synthesize α,α-disubstituted carbonyl derivatives, we recognized that this general mode of reactivity could potentially be extended to broad classes of electrophiles. For example, stereogenic aryl-substituted tertiary allylic alkenes are valuable but challenging compounds to synthesize using traditional asymmetric allylic substitution methods.[28] To address this challenge, we developed a Ni-catalyzed asymmetric reductive alkenylation (ARA) between alkenyl bromides and racemic benzylic chlorides, which provided products bearing aryl-substituted tertiary allylic stereogenic centers in excellent yields and enantiomeric excess under relatively mild conditions (Figure 4).[29] Similar to the acyl cross-coupling, BOX ligands were identified as promising candidates for inducing enantioselectivity. Further ligand development identified the cyclopropyl-linked indanyl-derived BOX ligand **L3** as optimal for both ee and enhanced cross-coupling selectivity; increased formations of homodimer derived from **13** were observed with other ligands. In contrast to acyl coupling, ethereal cosolvents led to reduced

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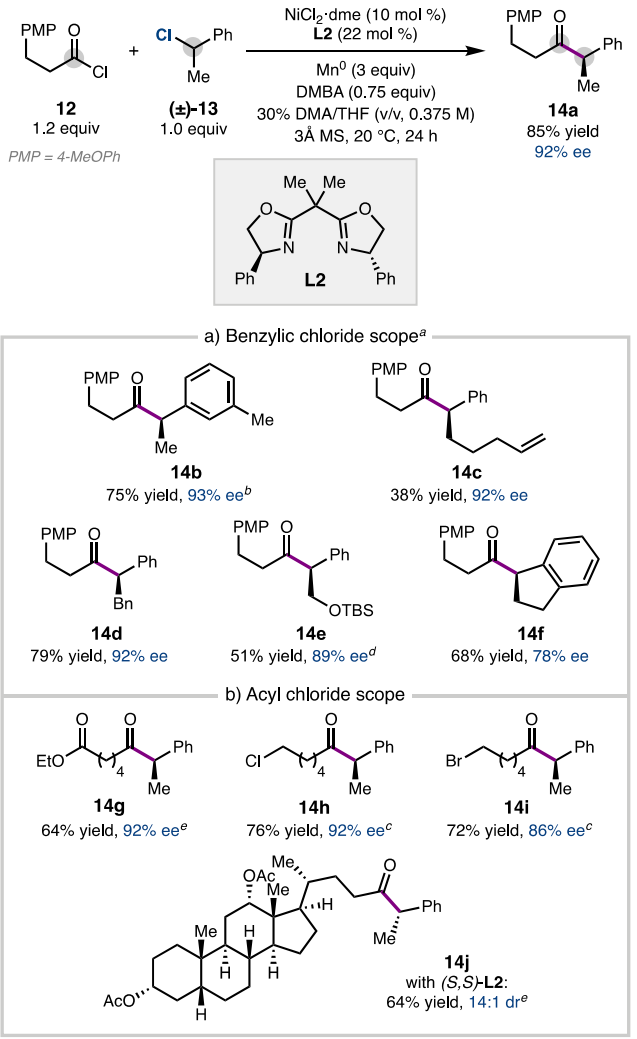

Figure 3. Enantioselective reductive cross-coupling of acyl chlorides and benzylic chlorides. [a]Run with 1.5 equiv of acyl chloride. [b]Run with 33 mol % *(R,R)*-**L2**. [c]Run in 20% v/v DMA/THF. [d]Run in 50% v/v DMA/THF. [e]Run in 10% v/v DMA/THF.

enantioselectivity. NaI was empirically found to increase the yield of the cross-coupling; it is reported that halide anions can influence the reduction potential, speciation, and coordination geometry of the Ni center, all of which can influence the oxidative addition and reduction steps.[30−32]

Under optimized conditions, the scope of C(sp^3) coupling partners was investigated, which demonstrated that a wide range of benzylic chlorides can be effectively coupled in high yield and enantioselectivity. Various β-substituted functional groups are also tolerated, with no erosion in enantioselectivity. In addition, both styrenyl bromides and nonconjugated alkenyl bromides are suitable coupling partners. However, trisubstituted olefins and *(Z)*-alkenyl bromides were identified as limitations.

The ARA reaction also provided an opportunity to investigate electrochemistry as a sustainable and scalable alternative to replace metal powder reductants.[33] In 2019, we demonstrated that the Ni-catalyzed ARA can be driven electrochemically, thereby eliminating the need for metal powder reductants (Figure 4).[3] Electrolysis of a solution containing alkenyl bromide **15**, benzylic chloride **13**, $NiCl_2$·dme, **L3**, and NaI in an undivided cell yielded product **16a** in 84% yield with 94% ee. The electrolysis was highly efficient with complete conversion after the theoretical required charge passed (2.0 F/mol). The choice of electrode materials played a crucial role for electrolysis with reticulated vitreous carbon (RVC) foam as the cathode and zinc as the anode providing the highest yield. Other sacrificial anode materials, such as Al and Mg, resulted in premature reaction termination. NaI served a dual role as both a reaction additive and optimal electrolyte for the system,[30−32] thereby giving rise to superior yields and enantioselectivities compared with other electrolytes like TBAI, $TBAPF_6$, and $NaPF_6$. When no current was passed, the product was obtained in 2% yield, which suggested that electricity was required to overcome the overpotential of the cell.

In 2018, we extended the C(sp^3) electrophile scope for this mode of reactivity to chloro(arylmethyl)silanes, which enabled the facile synthesis of enantioenriched allylic silanes (Figure 5).[34] Traditional methods employed for preparing chiral allylic silanes often involve the use of unstable Grignard reagents, which limits the functional group compatibility of the method.[35] We recognized that the Ni-catalyzed ARA could provide modular access to enantioenriched allylic silanes by coupling (chlorobenzyl)silanes with alkenyl halides.

The coupling of alkenyl bromide **15** and racemic chlorosilane **17** in the presence of $NiCl_2$·dme and the IndaBOX ligand (**L3**) proceeded with high enantioselectivity (96% ee) but low yield (20%), which we attributed to slow activation of the chlorosilane due to increased steric hindrance. By incorporating cobalt(II) phthalocyanine (CoPc) as cocatalyst to facilitate radical generation,[36] improved yield was achieved while high enantioselectivity was maintained.

A variety of (chlorobenzyl)trimethylsilanes coupled smoothly. Whereas strained silacyclobutane **18f** was synthesized with good yield and high enantioselectivity, lower yields were obtained with more sterically encumbered silanes (e.g., **18d,e**). Various functional groups on the alkenyl bromide coupling partner were well tolerated. While alkyl-substituted alkenyl bromides performed comparably with styrenyl bromides, (*Z*)-alkenes and highly substituted alkenyl bromides did not participate in the reaction. We envision that this highly enantioselective cross-coupling method of chiral allylic silanes synthesis could offer potential applications in stereospecific transformations.[37]

Following the initial success with acyl and vinyl electrophiles, we turned our attention to aryl electrophiles, which are critical building blocks for medicinal chemistry. The 1,1-diarylalkane motifs are found in many commercial pharmaceuticals and are typically obtained through asymmetric hydrogenation and conjugate addition methods. Fu and coworkers previously reported an enantioconvergent Negishi coupling of benzylic mesylates with aryl zinc halides but had limited success with heteroaryl substrates.[38]

To address this challenge, in 2017, our laboratory developed a Ni-catalyzed reductive cross coupling approach between aryl halides and racemic benzylic halides (Figure 6).[2] The choice of ligand was crucial for both reactivity and enantioselectivity, with bioxazoline (BiOX) ligands emerging as more promising than BOX and PhOX ligands, which had been used in our prior studies. A screen of BiOX ligands derived from commercially available amino alcohols revealed an interesting trend where increasing the substituent from *i*-propyl (^{i}Pr) to cyclopentyl (^{c}pent) to cyclohexyl (^{c}hex) increased both the yield and ee of the product. This led us to prepare several new

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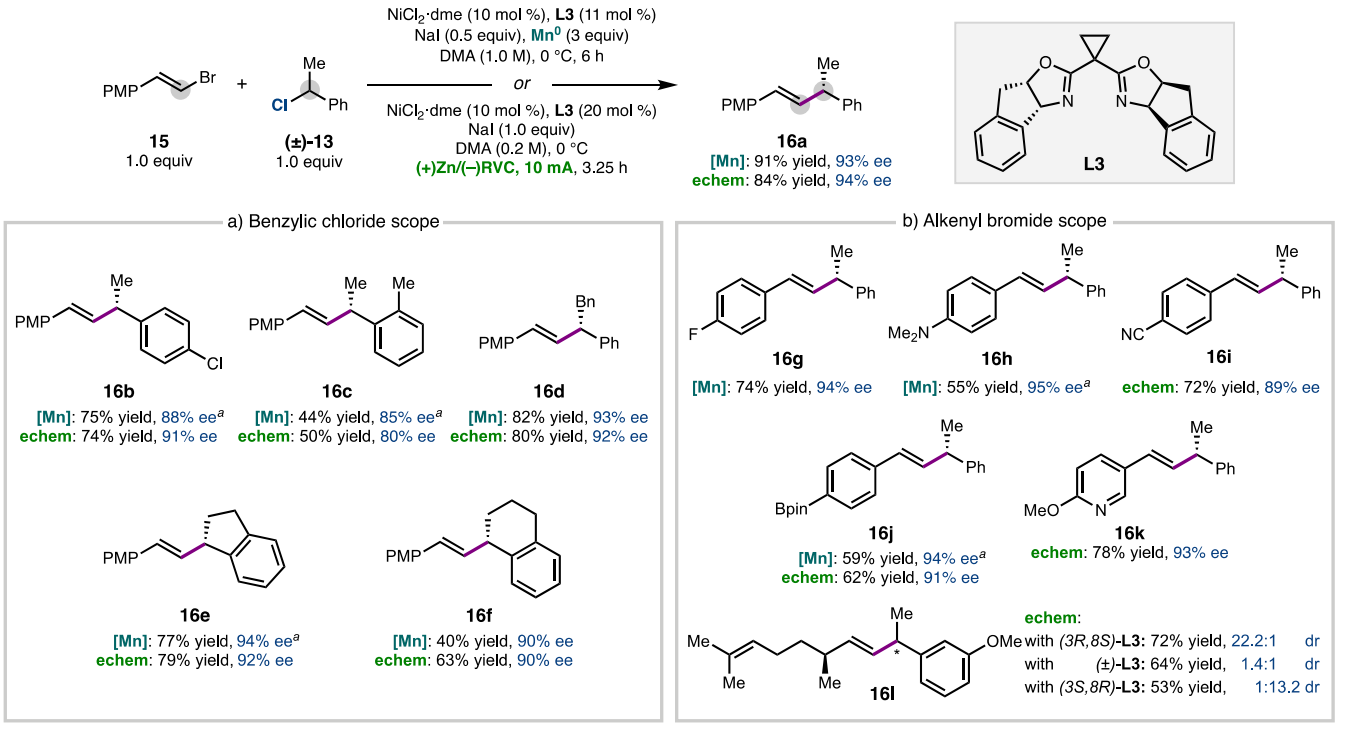

Figure 4. Enantioselective Mn^0-mediated reductive cross-coupling and electroreductive cross-coupling of alkenyl bromides and benzylic chlorides. [a]Run with 15 mol % $NiCl_2$·dme and 16 mol % **L3**.

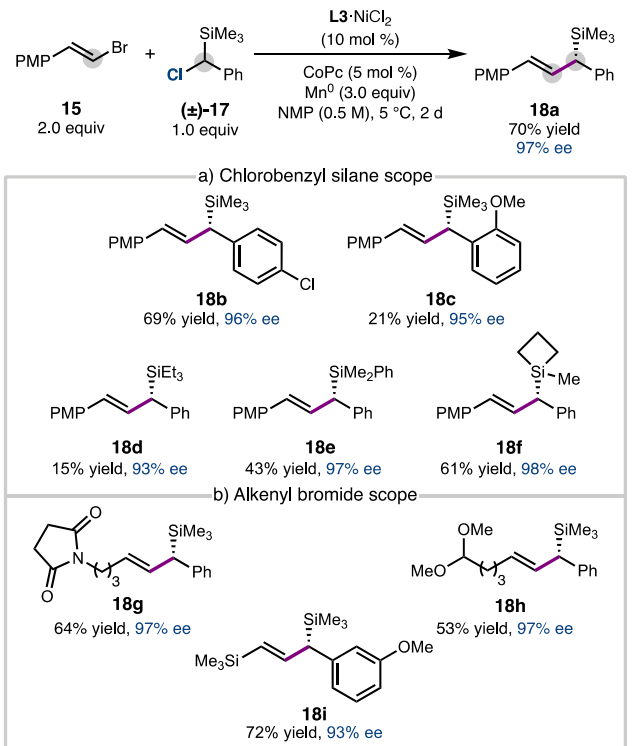

Figure 5. Enantioselective synthesis of chiral allylic silanes by reductive cross-coupling of alkenyl bromides and chlorobenzyl silanes.

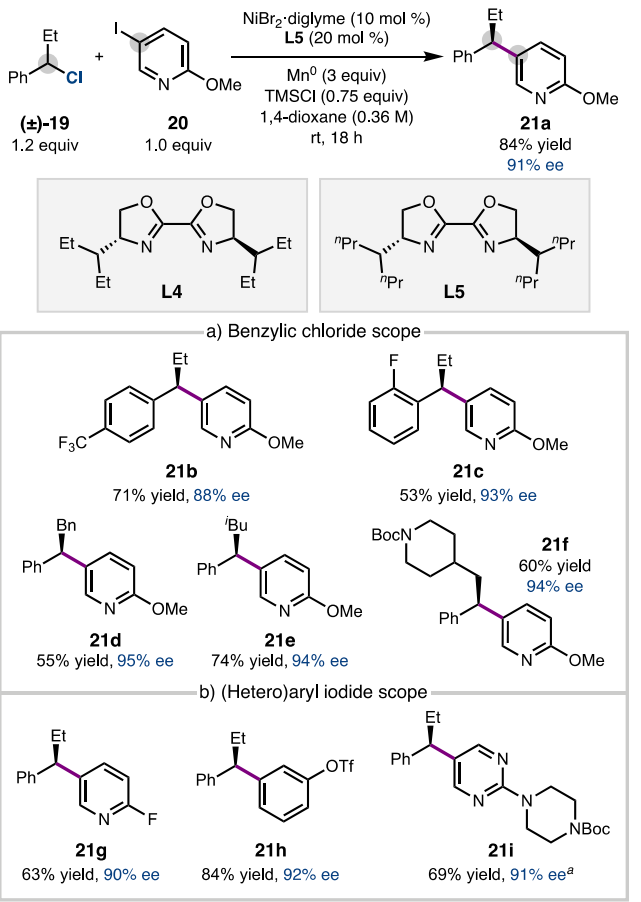

Figure 6. Enantioselective reductive cross-coupling of benzylic chlorides and (hetero)aryl iodides. [a]Run with 2.4 equiv of benzylic chloride **19**.

BiOX ligands, including the 3-pentyl- (**L4**) and 4-heptyl-BiOX (**L5**) ligands. The preliminary trend of increasing alkyl chain length leading to higher ee held true with **L5** providing **21a** in 84% yield with 90% ee.

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Various aryl and heteroaryl iodides with electron-rich or -poor groups were successfully coupled with high enantioselectivity (Figure 6). The cross-coupling was tolerant of aryl triflates (e.g., **21h**) and boronates. Substrates with branching β to the chloride performed well (e.g., **21e** and **21f**); however, steric bulk directly attached to the benzylic carbon (such as ^{t}Bu) was not tolerated. After the discovery of **L5**, various synthetic methods also reported the use of this ligand,[39,40] thereby demonstrating the importance of tuning ligand properties when considering new cross-electrophile couplings.

3.2. Other Benzylic Radical Precursors

Following the successful development of asymmetric reductive cross-coupling reactions using benzylic chlorides as C(sp^3) electrophiles, our group shifted focus to investigate the potential of redox-active *N*-hydroxyphthalimide (NHP) esters as coupling partners.[41,42] The goal was to overcome challenges associated with unstable or hard-to-synthesize alkyl chlorides; in particular, we anticipated better tolerance of electron-rich benzylic systems with the corresponding NHP ester (Figure 7).

During initial reaction development studies using alkenyl bromide **15** and racemic NHP ester **22**, we discovered that the organic reductant tetrakis(*N*,*N*-dimethylamino)ethylene (TDAE) performed better than Mn^0, in contrast to the related reaction of the benzylic chloride.[2] It was also determined that the use of a silyl halide was critical for product formation and that use of NaI also improved the yield. A key observation was that the corresponding alkenyl chloride could be formed through a Ni-catalyzed halide exchange if chloride was present in the reaction mixture, and this substrate was unproductive in further coupling.[43] Thus, the optimal conditions used **L3**·$NiBr_2$ as the precatalyst and TMSBr instead of TMSCl.

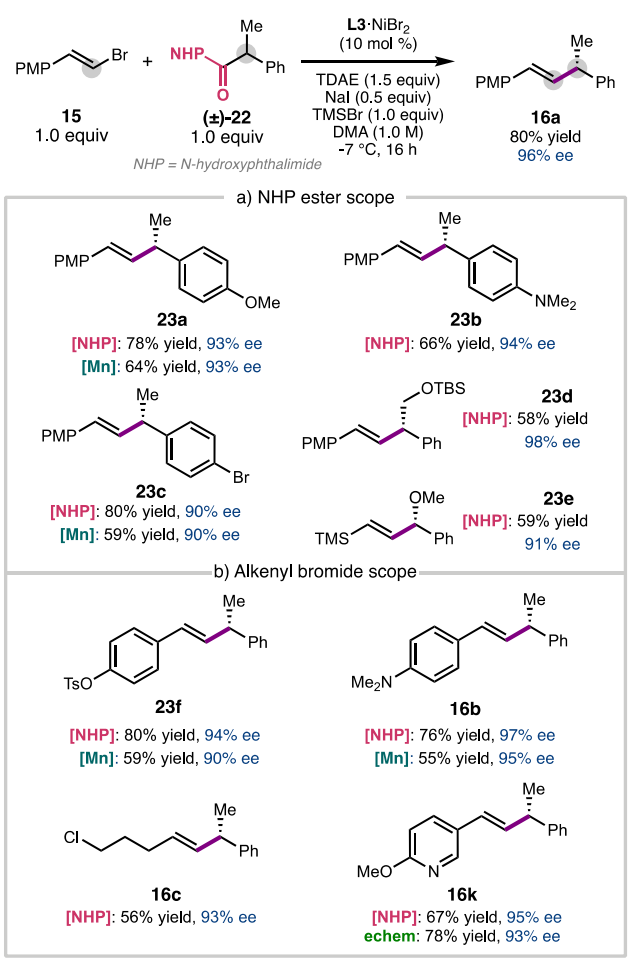

Figure 7. Enantioselective reductive cross-coupling of *N*-hydroxyphthalimide esters and alkenyl bromides. Yields of Mn^0-mediated[29] or electrochemically-driven[3] coupling of the corresponding benzylic chlorides are provided for comparison.

The cross-coupling between alkenyl bromides and NHP esters tolerated Lewis basic functional groups, such as anilines and nitriles, and non-styrenyl alkenyl bromides. Some NHP esters exhibit enhanced reactivity compared with the corresponding benzyl chlorides, and the method allows access to compounds that were challenging to prepare via previous coupling methods. Preliminary findings suggested the adaptability of these conditions for α-alkoxy NHP esters (**23e**) and other difficult substrates, thereby offering flexibility in choosing between NHP esters and benzylic chlorides on the basis of practical considerations like starting material availability.[44]

In 2022, a collaboration between Merck scientists and our group prompted us to develop a Ni/photoredox dual catalysis system between racemic *N*-benzylic trifluoroborates (BF_3K) and heteroaryl bromides to access *N*-benzylic heterocycles,[45] a common structural motif found in pharmaceuticals (Figure 8). While this approach is not a reductive coupling, it provides access to enantioenriched products related to the diarylalkanes shown in Figure 7. In this dual-Ni/photoredox catalysis system, the trifluoroborates serve as radical precursors[46] that can be captured by the nickel catalyst to generate the C(sp^2)−C(sp^3) bonds with enantiocontrol.

The initial reaction development focused on the cross-coupling between alkyl BF_3K **22** and 5-bromo-2-chloropyrimidine (**23**) using $NiCl_2$·dme as the nickel source, Ir[dF(CF$_3$)ppy]$_2$(bpy)PF_6 as the photocatalyst, and K_2HPO_4 as the base. Screening of chiral ligands using high-throughput experimentation (HTE) identified BiOX ligands **L5** and **L6** as the most promising, which resulted in an 80% yield and 97% ee under optimized conditions. These conditions were subsequently used to explore the scope of this transformation; BiOX **L5** was used in the aryl halide scope studies, but **L6** performed better for several alkyl BF_3K salts.

This reaction tolerated a range of substituents found in medicinal chemistry lead compounds, including pyrimidines, pyridines, fluorinated arenes, pyrazoles, and pyrroles, to provide products with high enantioselectivity and moderate to high yield. We observed that the products were generally formed in higher yields when the BF_3K salts were sparingly soluble, which is likely due to controlled release of the alkyl radical favoring coupling while reducing side reactions like protodeborylation and dimerization. As a result, the solvent served as an important handle for the reaction optimization.

3.3. Nonbenzylic C(sp^3) Electrophiles

A long-running goal for our Ni catalysis work has been to expand the scope of enantioselective reductive coupling to nonbenzylic electrophiles. Our first success in this direction was the Ni-catalyzed reductive arylation of α-chloronitriles (Figure 9)[47] where the nitrile groups serve as valuable precursors for a variety of functional groups. Initial investigations focused on the coupling of α-chloronitrile **25** with 3-iodoquinoline (**26**). An extensive investigation of ligands ultimately determined that electron-rich ligand DMMB-PHOX (**L7**) maximized product formation while

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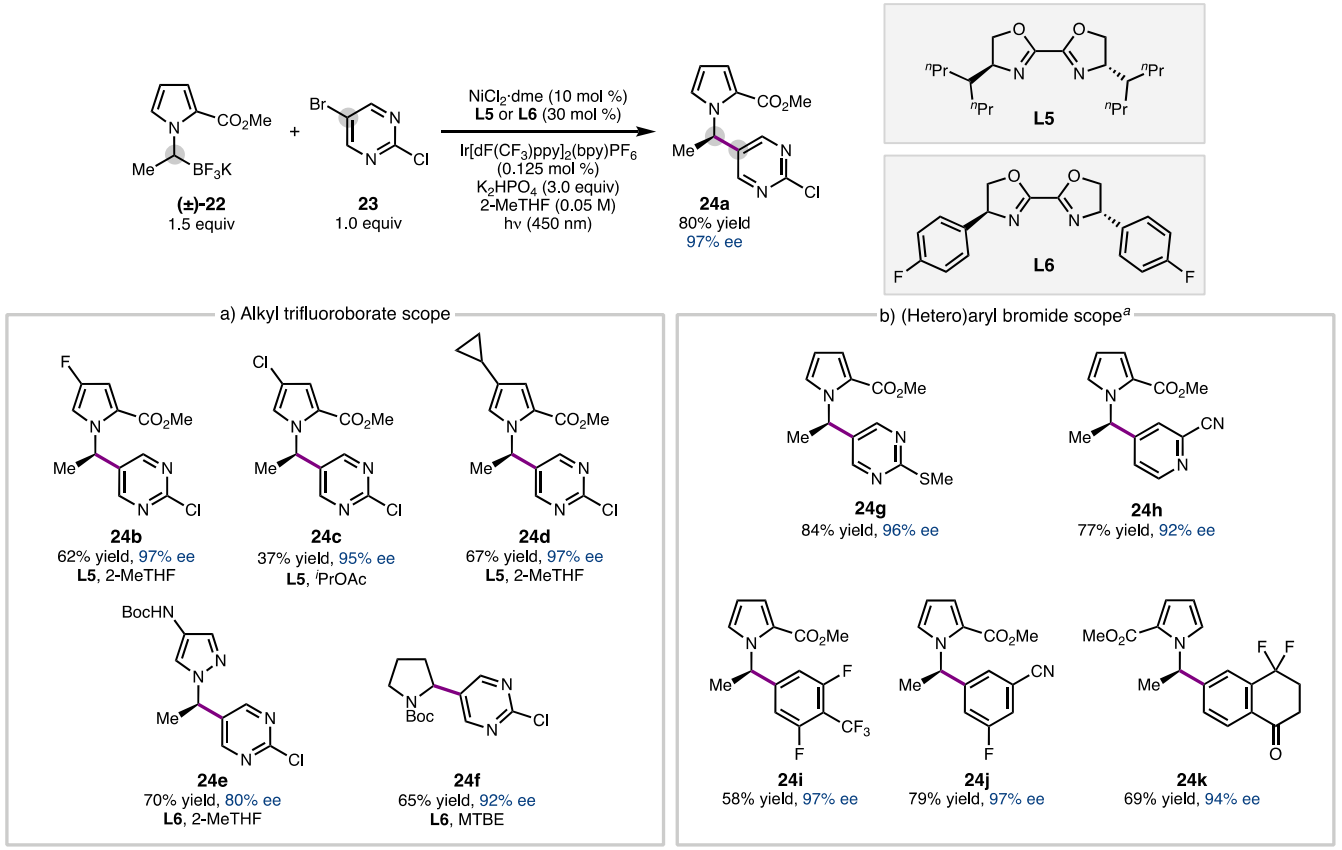

Figure 8. Enantioselective coupling of α-*N*-heterocyclic trifluoroborates and heteroaryl bromides using Ni/photoredox catalysis. [a]Run with **L5** as ligand.

minimizing the protodehalogenation of **25**. This choice of ligand provided the best combination of yield and enantioselectivity for the desired product **27a**.

A variety of α-chloronitriles and heteroaryl iodides were demonstrated to undergo cross-coupling to produce α,α-disubstituted nitriles with good yields and high enantioinduction. In several cases, the addition of 1.0 equiv of $NaBF_4$ further improved enantioselectivity and with comparable yield.[48] Different α-chloronitriles also exhibited good functional group tolerance, including carbamates, esters, and a primary alkyl chloride. This was the first Ni-catalyzed asymmetric reductive cross-coupling reaction that works with *N*- and *S*-heterocyclic coupling partners, which opened the possibility for related transformations with electrophiles containing Lewis basic functional groups.

In 2021, our group reported an asymmetric reductive cross-coupling method to access α-aryl stereogenic carboxylic acids utilizing α-chloroesters as C(sp^3) electrophiles (Figure 10).[49] This method offers an advantage by circumventing the need for pregenerated organometallic reagents and provides a route toward biologically active compounds, which are traditionally accessed through chiral resolution or chiral auxiliaries.

The study began with the exploration of the coupling between racemic α-chloroester **28** and pyridyl iodide **20**. Among various BiOX ligands, 4-heptylBiOX (**L5**) with branched alkyl chains outperformed other ligands, which resulted in a higher yield and enantioselectivity. Mn^0 was found to be more effective than Zn^0 or TDAE as the terminal reductant, and the addition of $NaBF_4$ was essential for product formation.[48]

A series of aryl iodides were coupled with α-chloroester **28** under standard conditions, thereby demonstrating tolerance for (hetero)aryl iodides with different electronics. Furthermore, the enantioselectivity of the reaction was sensitive to the structure of the α-chloroesters with increased enantioselectivity observed as the α-substituent increased in size (**29a**−**29c**). A multivariate linear regression (MLR) model was also employed to demonstrate the cooperative influence of the steric profiles between the ligand and the substrate, which provided insight toward further reaction development.[50,51]

4. OBSERVATIONS AND MECHANISTIC INSIGHTS

Since our initial report, a variety of Ni-catalyzed enantioselective RCC methods have been disclosed by our laboratory and others. An analysis of published reactions reveals that different electrophile pairs require different ligands for optimal reactivity and selectivity, but certain trends have emerged. For example, the ^{i}PrIndaBOX ligand (**L3**) initially disclosed for the reductive alkenylation of benzylic chlorides has proven optimal for a variety of additional Ni-catalyzed enantioselective alkenylation reactions.[52−54] Alternatively, BiOX ligands with branched alkyl substituents (e.g., **L5**) have proven versatile for a variety of enantioselective reductive arylation reactions.[40,55,56] The origin of this divergence in the ligand framework is likely not just related to enantioinduction but also reflects the different relative rates of oxidative addition of the respective electrophiles.

The use of heterogeneous reductants makes traditional kinetic analysis of RCCs more complicated, and in general, preparation of stable, isolable stoichiometric complexes with

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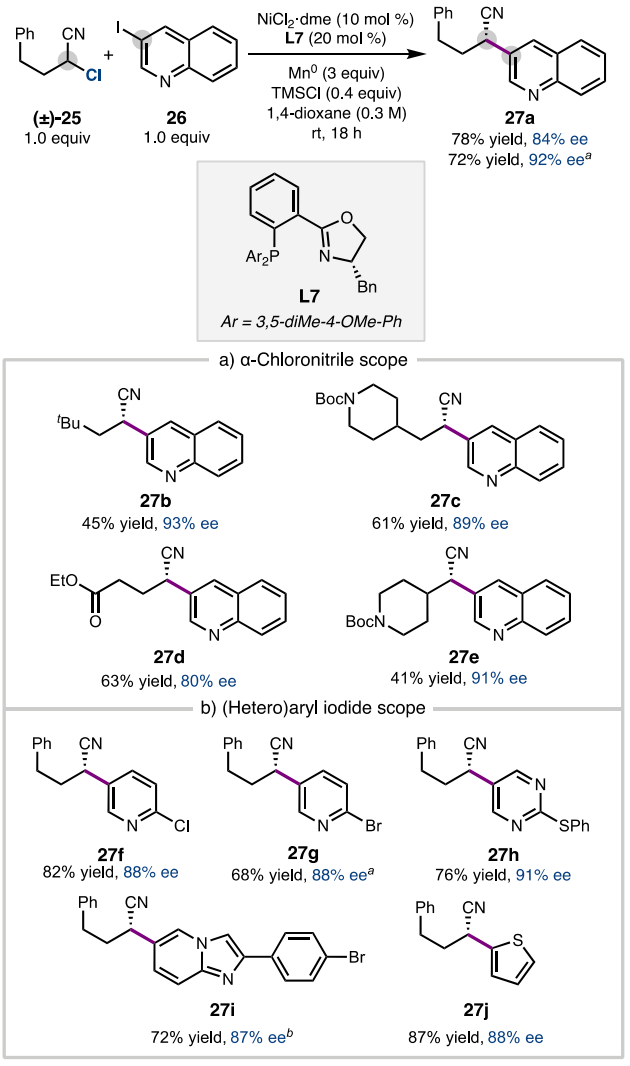

Figure 9. Enantioselective reductive cross-coupling of α-chloronitriles and heteroaryl iodides. [a]Run with 1.0 equiv of $NaBF_4$ added. [b]Run with 2.0 equiv of heteroaryl iodide.

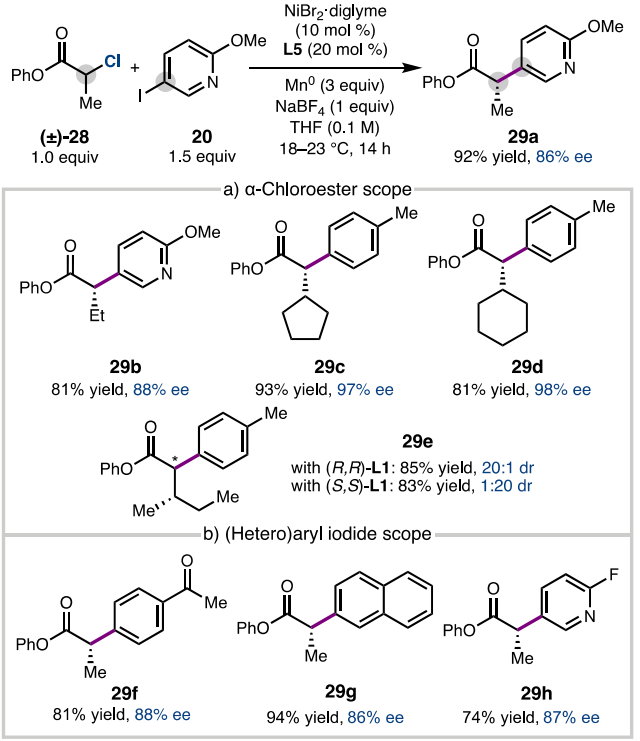

Figure 10. Enantioselective reductive cross-coupling of α-chloroesters and heteroaryl iodides.

chiral ligands, such as BOX and BiOX, has been challenging. Nonetheless, recent studies by Diao et al.[32,57,58] and our lab[4] have provided insights on the mechanisms of the enantioselective reactions with some common themes. The $Ni^{II/I}$ reduction potentials of several well-characterized BOX and BiOX complexes have been determined using cyclic voltammetry (CV), which typically exhibit electrochemically irreversible reduction waves due to rapid halide loss upon one-electron reduction (Figure 11a).[4,59,60] These CV studies determined that for both the BiOX·NiX_2 and BOX·NiX_2 complexes, $Ni^{I/0}$ reduction requires potentials more negative than −2.0 V, which suggests that **L**·Ni^0 is likely not accessible under standard reaction conditions using Mn^0, Zn^0, or TDAE as reductants. This is inconsistent with early mechanistic proposals of Ni-catalyzed RCCs with BOX and BiOX ligands that invoked oxidative addition of the $C(sp^2)$ electrophile by L·Ni^0 complexes. Investigations by Diao et al. using isolable model compound **L9**·Ni^IBr demonstrated that it activates mesityl bromide to arrive at a mixture of **L9**·Ni^{II}(Mes)Br and **L9**·$Ni^{II}Br_2$ (Figure 11b).[59] Consistent with Diao et al.'s studies, we used CV to show that upon reduction of **L3**·$Ni^{II}Cl_2$, the presumed **L3**·Ni^ICl reacts with alkenyl halide **15** with a concentration-dependent increase in current (Figure 11b).[4] Taken together, these and other mechanistic studies suggest that both the BOX·Ni-catalyzed reductive alkenylation and BiOX·Ni-catalyzed arylation are unlikely to involve Ni^0 species, but instead, **L**·Ni^IX species activates the $C(sp^2)$ electrophile to arrive at an **L**·$Ni^{II}[C(sp^2)](X)$ resting state, presumably by reduction of a transient Ni^{III} species.[61,62]

Although there is some mechanistic coalescence between the BiOX-catalyzed reductive arylation and the BOX-catalyzed alkenylation with respect to activation of the $C(sp^2)$ electrophile (e.g., **I** to **II**, Figure 11d), there are a number of mechanistic pathways by which $C(sp^3)$ electrophile activation can proceed. The stereoconvergent nature of the enantioselective reductive cross-couplings is most consistent with formation of an alkyl radical intermediate (which has also widely been supported by radical clock substrates, as well as radical trapping studies); however, the pathway by which these radicals form can vary. Recent mechanistic studies by our laboratory determined that for the reductive alkenylation catalyzed by **L3**·$Ni^{II}X_2$ complexes, the mode of $C(sp^3)$ electrophile activation depends on the identity of the electrophile and the reductant.[4] In the TDAE-mediated ARA of NHP esters, the combination of TDAE and TMSBr serves to generate the radical in the turnover-limiting step. This was further supported by the detection of homodimer **30** when **22** was treated with TDAE in the presence of TMSBr and in the absence of Ni (Figure 11c). It is proposed that TMSBr serves as a Lewis acid to lower the reduction potential of the NHP ester ($E_{p/2}$ = −1.62 V vs $Fc^{0/+}$), thereby rendering the reduction by TDAE ($E_{1/2}$ = −1.11 V vs $Fc^{0/+}$) possible. The rate of radical generation from **22** can be controlled by using various Lewis acid additives, presumably by modulating the equilibrium concentration of the NHP ester−Lewis acid adduct. Consistent with this proposal, for silyl halide additives,

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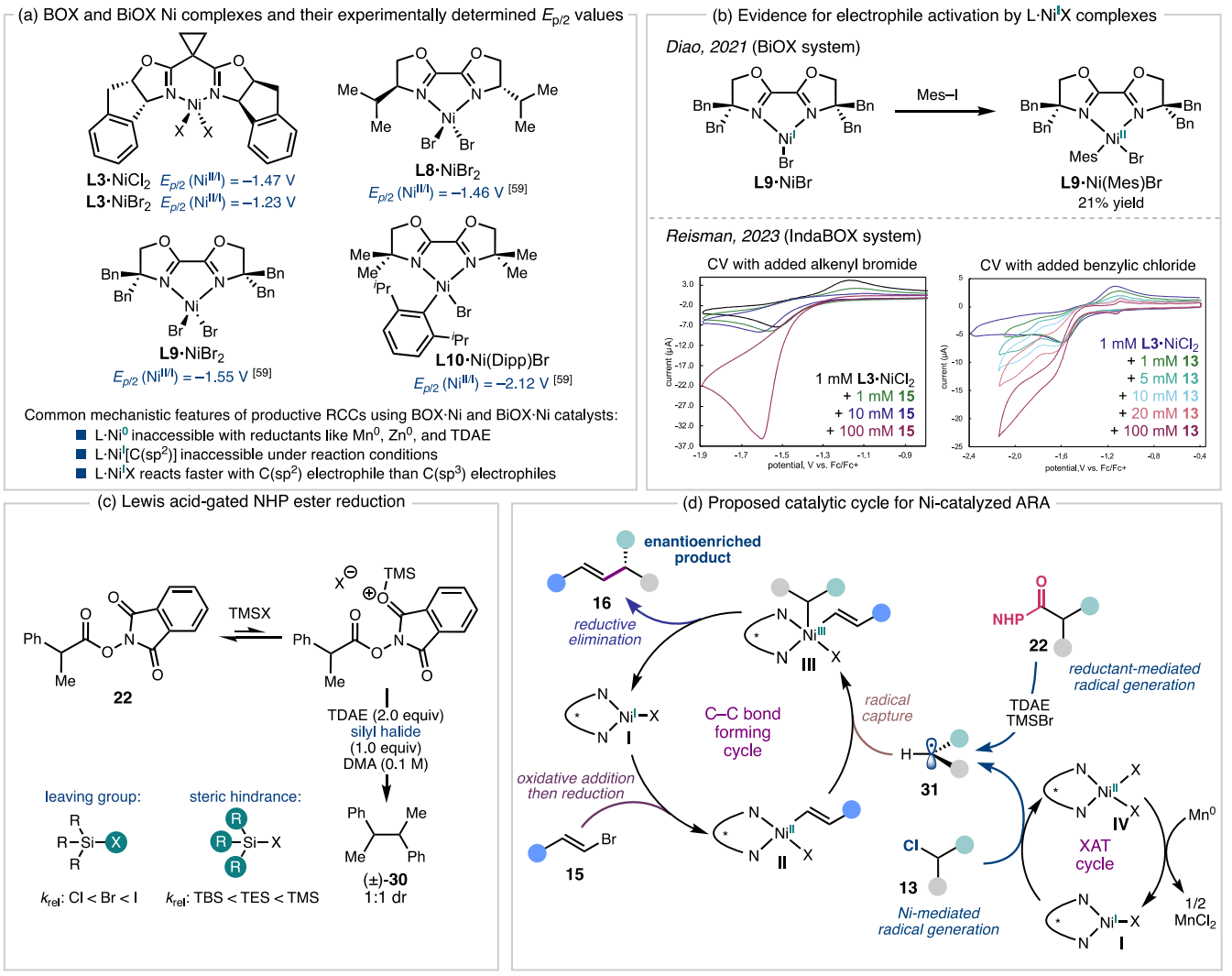

Figure 11. (a) Literature-reported L·Ni^{II} complexes and their experimentally determined $E_{p/2}$ values. (b) Evidence for electrophile activation by L·Ni^{I} complexes. (c) Lewis acid-gated NHP ester reduction and observed trends. (d) Summary of proposed catalytic cycle for Ni-catalyzed ARA.

smaller steric hindrance (TMS > TES > TBS) and better leaving groups (I > OTf > Br > Cl) favor faster activation of the NHP ester. Tuning the rate of radical generation by changing the Lewis acid was used to optimize the product yield at lower catalyst loadings, thereby highlighting the importance of rate matching between oxidative addition of the alkenyl bromide to the nickel catalyst and radical generation from the NHP ester.

Whereas Ni was not involved in the NHP ester activation, our studies suggest that the **L3**·Ni^{I}X does activate the benzylic chloride.[4] Using CV, concentration-dependent currents were observed when **13** was introduced to the solution of **L3**·Ni^{II}Cl$_2$ in DMA, which indicates that the reduced **L3**·Ni^{I}Cl can activate **13** to form benzyl radical **31** (Figure 11b). In the presence of 100 mM of both alkenyl bromide **15** and benzylic chloride **13**, a catalytic current consistent with **15** was observed, which suggests the faster activation of **15** under otherwise identical conditions.[58,63] This is also consistent with the Mn^0-mediated Ni-catalyzed homodimerization reactions where **15** displayed a faster activation rate than **13**.[4] On the basis of these observations and detection of an **L3**·Ni^{II}(alkenyl)X resting state by NMR, mechanisms for the TDAE- and Mn^0-mediated Ni-catalyzed ARAs were proposed (Figure 11d). Whereas the C–C bond forming cycle follows the same pathway for both reactions, the generation of the C(sp^3) radical (**31**) occurs by distinct mechanisms: by TDAE reduction in the case of NHP esters (e.g., **22**) or by **L3**·Ni^{I}X-catalyzed halide atom abstraction (XAT) in the case of benzylic chlorides (e.g., **13**). In the Mn^0-mediated coupling, the observed reactivity of **L3**·Ni^{I}X with both **15** and **13** suggests that this complex is partitioned between two processes: the oxidative addition/reduction of alkenyl bromide **15** and the halide atom abstraction (XAT) of benzylic chloride **13**. This investigation sheds light on the intricate mechanisms governing these reactions and underscores the importance of balanced activation rates of electrophiles, thereby providing guidance for future developments in RCCs.

This case study is just one example in which there is a mechanistic change for the mode of activation of two electrophiles under quite similar reaction conditions. Many Ni-catalyzed reductive coupling reactions are proposed to involve halide abstraction by Ni^{I} complexes, and we also note that the same elementary step is proposed in many Ni-catalyzed redox-neutral couplings, such as those extensively investigated by Fu.[24] The identity of the ligand can modulate the redox potential of the Ni^{I} species, which in turn can effect

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which C(sp^3) electrophiles can be activated through an XAT process. We note that computational studies from Hadt et al.[60] and experimental studies by Diao and co-workers[59] suggest that reduction of L·Ni^{II}[C(sp^2)]X to the corresponding L·Ni^{I}[C(sp^2)] species requires strongly reducing potentials for BOX- or BiOX-supported complexes. It is unlikely that L·Ni^{I}[C(sp^2)] species, which have been shown for other ligand classes to promote XAT, can be effectively generated using standard reductants like Mn^0 or Zn^0 when BiOX or BOX ligands are employed. This might be a contributing reason to why the scope of Ni-catalyzed enantioselective RCC reactions has been largely limited to activated C(sp^3) electrophiles, such as those described in this account.

5. CONCLUSION AND OUTLOOK

In summary, over the past decade, our laboratory has produced a collection of Ni-catalyzed enantioselective reductive coupling reactions. We have emphasized the advantages of utilizing easily accessible and stable electrophiles, which serve as versatile building blocks for synthesizing a wide range of enantioenriched scaffolds with exceptional efficiency. Moreover, our exploration has extended beyond benzylic chloride coupling partners to include C(sp^3) electrophiles, such as NHP esters and α-chloroesters, complemented by utilizing BF_3K salts under metallaphotoredox conditions. This expansion broadens the horizons of Ni-catalyzed cross-coupling reactions and offers exciting opportunities for the synthesis of diverse and intricate molecules.

Additionally, our research underscores the pivotal role of selecting chiral ligands in shaping the cross-selectivity and enantioselectivity of the reaction outcomes. We have also introduced alternatives to traditional metal powder reductants, such as TDAE, and explored the potential of electrochemistry, which can provide advantages over heterogeneous reductants. Furthermore, our investigations have delved into the intricate mechanistic variations that arise when employing different electrophiles and reductants. These insights have been instrumental in optimizing cross-selectivity and improving overall reaction outcomes, which highlight the importance of rate matching between electrophiles.

Nevertheless, it is crucial to acknowledge that several challenges remain. Techniques, such as ligand parametrization through multivariate linear regression analysis, offer a promising path to unravel complex data patterns and provide insights into reactivity and stereoselectivity. Quantifying electrophile activation rates is pivotal for assessing cross-selectivity, and combining multivariate linear regression with electroanalytical tools, like cyclic voltammetry, enhances our understanding of oxidation rates across diverse electrophiles.[64] This comprehensive understanding will enable informed ligand selection to optimize cross-selectivity and enantioselectivity.

Ultimately, while enantioselective cross-couplings of *sec*-alkyl partners with C(sp^2) partners have been extensively investigated, the corresponding asymmetric cross-coupling reactions involving *tert*-alkyl partners or unstabilized *sec*-alkyl partners remain largely uncharted territory.[65,66] We anticipate that continuous development will expand the applications of Ni-catalyzed enantioselective RCCs in the context of complex molecule synthesis, thereby offering substantial opportunities for significant synthetic progress and revolutionizing carbon–carbon bond construction.

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CRediT: **Li-Ming Chen** writing-original draft, writing-review & editing; **Sarah E. Reisman** conceptualization, funding acquisition, project administration, writing-original draft, writing-review & editing.

Notes

The authors declare no competing financial interest.

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