Perspective

Nickel-Catalyzed Enantioselective Reductive Cross-Coupling Reactions

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ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.0c01842 • Publication Date (Web): 24 Jun 2020

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Supporting Information Placeholder

ABSTRACT: Nickel-catalyzed reductive cross-coupling reactions have emerged as powerful methods to join two electrophiles. These reactions have proven particularly useful for the coupling of *sec*-alkyl electrophiles to form stereogenic centers; however, the development of enantioselective variants remains challenging. In this Perspective, we summarize the progress that has been made toward Ni-catalyzed enantioselective reductive cross-coupling reactions.

Keywords: Nickel-catalysis, enantioselective, reductive cross-coupling, asymmetric catalysis, cross-electrophile coupling

I. Introduction

Transition metal catalysis has unlocked new modes of reactivity that have redefined the synthetic strategies used for the preparation of enantioenriched molecules. Cross-couplings constitute one subset of transition metal-catalyzed reactions and canonically refer to the coupling of an organic electrophile (typically an organic halide or pseudohalide) with an organometallic reagent. The use of C(sp^3) coupling partners has traditionally been limited by slow oxidative addition or transmetalation, as well as decomposition via rapid β-hydride elimination in the presence of palladium or other precious metals.[1] Employing base metal catalysts, such as nickel, for *sec*-alkyl cross-couplings can circumvent these challenges.[2]

Recently, Ni-catalyzed reductive cross-coupling (RCC) reactions, which join two electrophiles in the presence of a terminal reductant, have emerged as promising methods for the enantioselective coupling of C(sp^3) electrophiles.[3] RCC reactions typically proceed under less basic conditions at ambient temperatures (between 0 and 40 °C), which allows broad functional group tolerance and avoids racemization of newly formed stereocenters. Given that halide electrophiles are often used as precursors to the organometallic coupling partners for canonical cross-coupling reactions, and the wide commercial availability of the halogenated building blocks, the direct use of these electrophiles in RCCs is appealing.[4] RCC reactions can be particularly advantageous for intramolecular C–C bond formation, because they obviate the need to install both an electrophile and an organometallic functional group in the same starting material.[5]

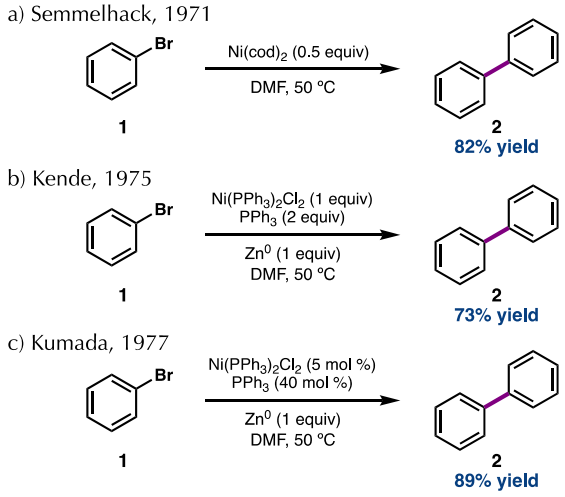
Several challenges exist that hinder development of reductive cross-coupling reactions. Most methods require a stoichiometric amount of heterogeneous metal dust as a terminal reductant, which renders them sensitive to stir rates, in addition to metal purity and mesh size.[6,7a] The generation of metal salt byproducts, as well as the common use of amide solvents, reduces the sustainability of RCCs and can introduce reproducibility issues.[8,9] Although RCCs are widely used by medicinal chemists, advances in reductant and solvent choices will be required for application of this technology in process chemistry.[8,10,11]

In this Perspective, we discuss the development of enantioselective RCCs catalyzed by nickel that employ a terminal reducing agent. Related reactions that are stereospecific,[3e] that utilize photoredox co-catalysis,[12,13] or that involve 1,2-addition to polar π-systems (e.g. the Nozaki–Hiyama–Kishi coupling)[14] have been reviewed elsewhere.

II. Historical Context for RCC Reactions

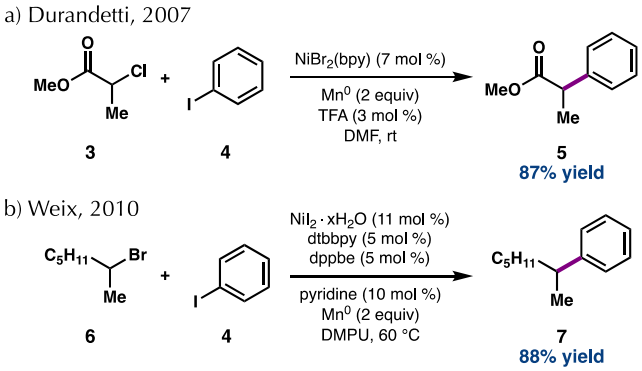
Seminal reports by Semmelhack,[15] Kende,[16] and Kumada[17] demonstrated the ability of nickel to mediate the reductive homocoupling of C(sp^2) halide electrophiles to form biaryl products (**Scheme 1**).[18] However, extension of this reactivity from homocoupling to the cross-coupling of distinct partners remained elusive for several decades, due to the challenges associated with achieving cross-selectivity.[19] When employing two electrophilic coupling partners, a large excess of the less-reactive electrophile can be one way to outcompete the homocoupling process. A more efficient strategy is to sequence the reactions of the two electrophiles, such as by leveraging the different rates of oxidative addition of a C(sp^2) or C(sp^3) electrophile to different Ni species in the catalytic cycle.[20,21] If the two electrophiles react selectively with distinct oxidation states of the Ni catalyst, then sequential oxidative addition events can afford the desired cross-coupled product and minimize homocoupled dimers.[22] Thus, optimization campaigns for these reactions often focus on how reaction parameters affect the distribution of the desired cross-coupled product to homodimers and reduction products.

Scheme 1. Seminal reports of Ni-mediated reductive homocoupling.



Much effort has focused on the Ni-catalyzed cross-selective couplings of *sec*-alkyl electrophiles. In 2007, Durandetti and coworkers reported the Ni-catalyzed reductive C(sp^2)–C(sp^3) cross-coupling of α-chloroesters and aryl iodides using Mn^0 as a terminal reductant (**Scheme 2a**).[23] Weix and coworkers followed in 2010 with the RCC of a *sec*-alkyl bromide and an aryl iodide, also utilizing a Ni(II) catalyst and bipyridine-based ligand (**Scheme 2b**).[24] Over the last decade, ongoing research has greatly expanded the scope of RCC reactions that use Mn^0 or Zn^0 as the terminal reductant to include many different *sec*-alkyl electrophiles, including those generated in situ from olefins.[25,26]

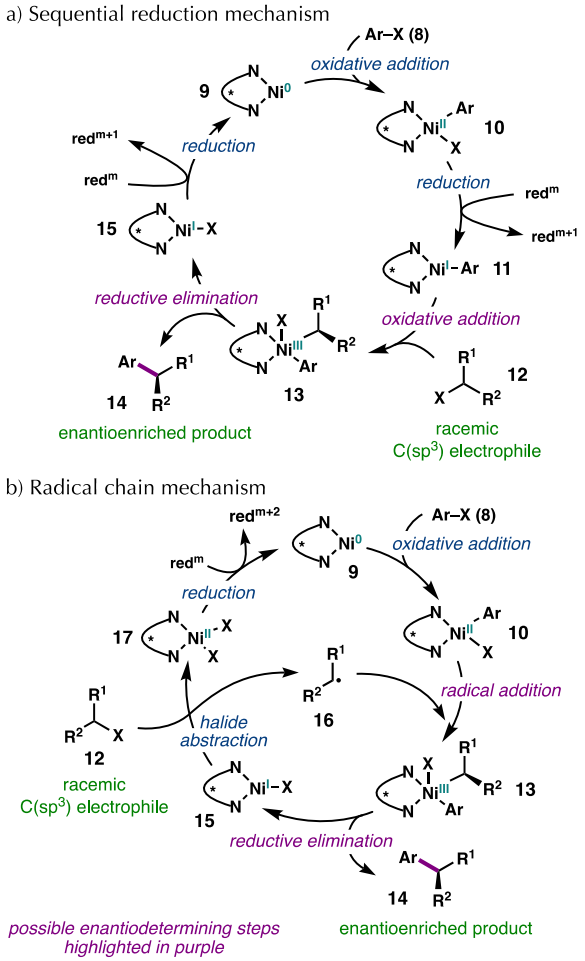
Scheme 2. First reports of Ni-catalyzed cross-coupling of C(sp^2) and C(sp^3) electrophiles with metal reductants.



III. Mechanistic Considerations

Before the last decade, all examples of Ni-catalyzed asymmetric cross-couplings fell into the category of redox-neutral transformations. Extensive methods development and mechanistic investigations by Fu and coworkers on the enantioconvergent cross-coupling of *sec*-alkyl electrophiles have demonstrated the feasibility of generating an alkyl radical through halide abstraction by a Ni(I) complex and engaging this species in enantioselective catalysis.[27,28] Our group and others hypothesized that mechanistic similarities with enantioconvergent redox-neutral couplings could be leveraged toward the development of enantioselective RCC reactions.

Figure 1. Proposed mechanistic hypotheses.



Investigations of Ni-catalyzed reductive cross-couplings have been conducted by several groups and can be organized into two limiting possibilities that are referred to as 1) the sequential reduction mechanism and 2) the radical chain mechanism (**Figure 1**).[29,30] In a sequential reduction mechanism, it is proposed that the C(sp^2) electrophile (shown as aryl halide **8** for clarity) undergoes oxidative addition to a Ni(0) species (**9**) to afford Ni(II)–aryl complex **10**,[31] which is then reduced by a metal reductant to **11** (**Figure 1a**).[32,33] The Ni(I)–aryl complex (**11**) can then effect halide abstraction from a racemic *sec*-alkyl electrophile (**12**)[34] to generate a prochiral radical that undergoes recombination with the metal center to give a Ni(III) intermediate (**13**).[35] Subsequent reductive elimination affords the enantioenriched product (**14**) and Ni(I)–halide complex **15**, which can be reduced to regenerate the Ni(0) catalyst (**9**) and close the catalytic cycle.

The second proposed mechanism involves a radical chain process (**Figure 1b**).[36] The C(sp^2) electrophile (**8**) undergoes oxidative addition to Ni(0) complex **9**. The resulting Ni(II) intermediate (**10**) then combines with a cage-escaped *sec*-alkyl radical (**16**) to give Ni(III) complex **13**,[37] which upon reductive elimination gives the enantioenriched product (**14**) and Ni(I)–halide **15**.[27] The resulting Ni(I)–halide species (**15**) can abstract a halide from the C(sp^3) electrophile (**12**) to generate long-lived *sec*-alkyl radical **16**.[38] Finally, the Ni(II)–dihalide species (**17**) can be reduced, regenerating the Ni(0) catalyst (**9**) to close the catalytic cycle.

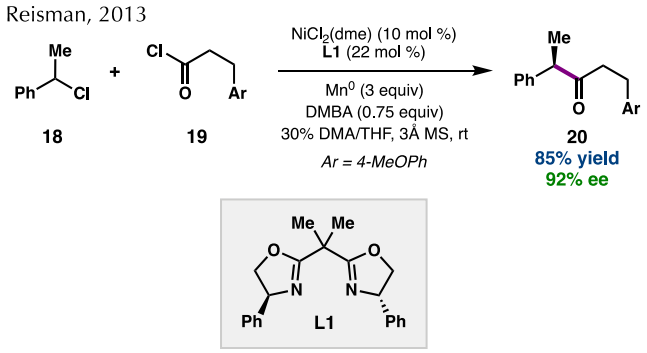
A major difference between the sequential reduction and radical chain mechanisms is the lifetime of the alkyl radical generated by halide abstraction, which either reacts via a radical rebound process in the solvent cage (sequential reduction mechanism) or is long-lived and escapes the cage (radical chain reaction mechanism). Experimental and computational data support each mechanism in different systems, suggesting that the mechanism of Ni-catalyzed reductive cross-couplings varies with different substrates, ligands, and reaction conditions.[21] It is also possible that similar mechanisms are operative where the C(sp^2) electrophile oxidatively adds to a Ni(I) complex, and the cycle does not proceed through reduction of the catalyst to Ni(0).[7,26d,39] In any of these scenarios, the enantiodetermining step could be radical addition to a Ni(II) complex to form a single diastereomer of a Ni(III) complex, followed by facile reductive elimination.[28b] Alternatively, if radical addition to Ni(II) is reversible, then reductive elimination from the Ni(III) species could be the enantiodetermining step.[13a,35]

IV. Ni-Catalyzed Enantioconvergent RCC Reactions of C(sp^2) and C(sp^3) Electrophiles

In 2013, our laboratory reported the first highly enantioselective Ni-catalyzed reductive cross-coupling (**Scheme 3**).[40] In this reaction, racemic benzylic chlorides were cross-coupled with acyl chlorides using a Ni(II) pre-catalyst, a chiral bis(oxazoline) (BOX) ligand (**L1**), and Mn^0 as the terminal reductant. High enantioselectivity but low reactivity was observed in THF, whereas DMA provided higher reactivity, but also more homocoupling sideproduct formation. A mixed solvent system of DMA and THF provided the

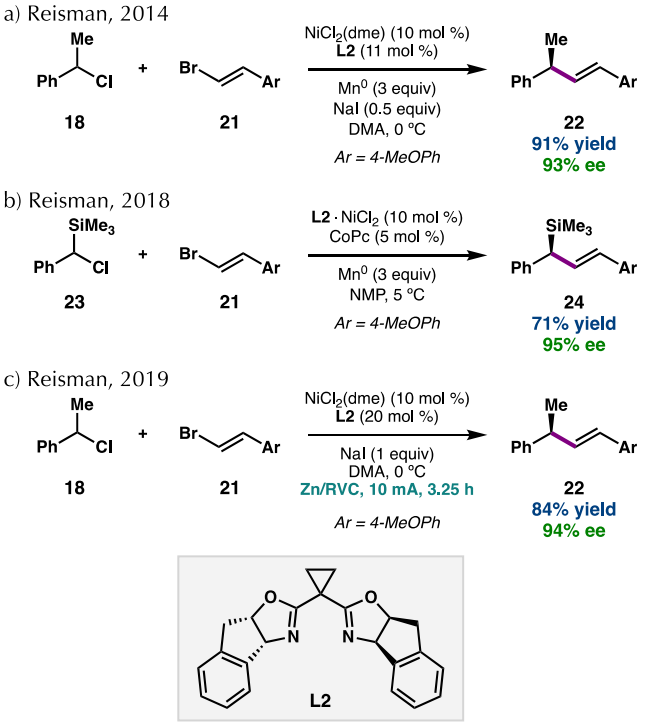
optimal balance of reactivity and selectivity. Importantly, we found that the addition of dimethylbenzoic acid (DMBA) suppressed homocoupling of the C(sp^3) electrophile. A variety of functional groups were tolerated on both coupling partners, providing the products in high yield and enantiomeric excess (ee).

Scheme 3. First report of enantioconvergent RCC.



In 2014, we reported a related reaction, in which alkenyl bromides undergo Ni-catalyzed enantioselective RCC with benzylic chlorides (**Scheme 4a**).[41] Chiral BOX **L2** was identified as the optimal ligand for this reaction, giving the products bearing allylic stereocenters in excellent ee when the reaction was conducted in DMA. NaI was determined to be an important additive in the reaction, improving the yield of **22** and decreasing the formation of the dibenzyl homodimer. NaI has been suggested to enhance reactivity in reductive cross-couplings through acceleration of electron transfer between Mn^0 and Ni or by in situ formation of iodide electrophiles.[42] In 2018, this mode of reactivity was extended to chloro(arylmethyl)silanes, allowing access to enantioenriched allylic silanes (**Scheme 4b**).[43] Co-catalysis with cobalt phthalocyanine (CoPc) was required for efficient coupling of these bulky silyl electrophiles, presumably to facilitate radical generation.[44]

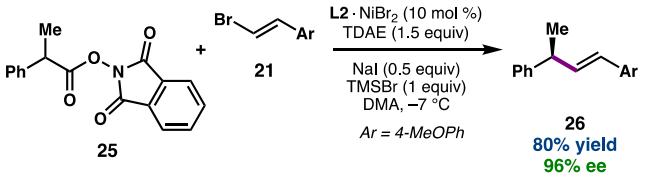
Scheme 4. Enantioconvergent RCCs of alkenyl bromides.



While attempts to render reductive couplings more sustainable and scalable have been reported for racemic coupling reactions, comparable asymmetric efforts are few in number.[8,10,11] We have demonstrated that Ni-catalyzed enantioselective reductive alkenylation reactions, such as that between **18** and **21** to give **22**, can be driven electrochemically (**Scheme 4c**).[45] In addition, for the Ni-catalyzed asymmetric reductive alkenylation of *N*-hydroxyphthalimide (NHP) esters,[46,47] the best results were obtained with the organic reductant tetrakis(dimethylamino)ethylene (TDAE);[8,48] Mn^0 and Zn^0 as the terminal reductants provided significantly lower yield (**Scheme 5**).[49] The coupling of NHP esters was advantageous for improving the scope of electron-rich benzylic systems, where the corresponding benzylic chlorides were unstable. In the NHP ester couplings, a significant amount of (*E*)-1-(2-chlorovinyl)-4-methoxybenzene was observed when using a chloride-containing precatalyst or TMSCl as an additive, presumably due to a Ni-catalyzed halide exchange process.[50] This alkenyl chloride was inert in the cross-coupling reaction; thus, it was necessary to eliminate all sources of chloride in the catalyst and additives to improve the yield.

Scheme 5. Enantioconvergent reductive decarboxylative cross-coupling.

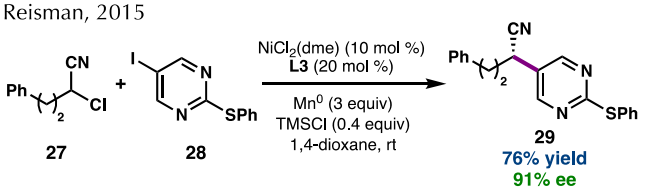
Reisman, 2017

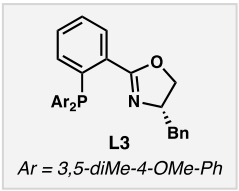


Despite early success with activated C(sp^3) coupling partners, variation of the C(sp^2) electrophile necessitated chiral ligands outside of the BOX family. In 2015, we published a Ni-catalyzed asymmetric RCC of α-chloronitriles and (hetero)aryl iodides (**Scheme 6**).[51] This reaction required a phosphinooxazoline (PHOX) ligand (**L3**) and provided high yields and enantioselectivities of the secondary nitrile products when TMSCl was used as an additive.[38,52] In the case of diarylalkane formation, the development of a new bioxazoline (BiOX) ligand bearing secondary alkyl substituents with long alkyl chains (**L4**) was required to obtain good yield and enantioselectivity (**Scheme 7a**).[53] Interestingly, the coupling of either α-chloronitriles or benzylic chlorides with (hetero)aryl iodides worked optimally under similar reaction conditions, but required a different ligand. This highlights the importance of tuning the ligand properties when investigating new electrophile combinations in enantioselective RCC reactions.

Scheme 6. Enantioconvergent RCC of α-chloronitriles.

Reisman, 2015

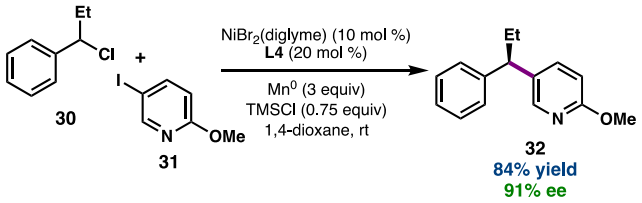




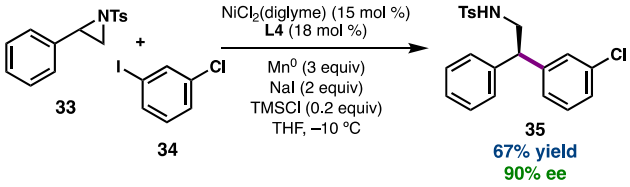
Contemporaneously to our development of the diarylakane formation in **Scheme 7a**, the Doyle and Sigman groups published an enantioselective reductive cross-coupling of racemic styrenyl-derived aziridines and aryl iodides, invoking a similar stereoconvergent mechanism (**Scheme 7b**).[54] Using **L4**, developed by our lab, 2-arylphenethylamine products were formed with high levels of enantioselectivity. Multivariate analysis of the effect of chiral BiOX ligands on the reaction revealed that ligand polarizability influences the enantioselectivity, suggesting the presence of noncovalent interactions, such as dispersion forces or CH–π interactions, in the selectivity-determining transition state.

Scheme 7. Enantioconvergent RCCs with a novel BiOX ligand.

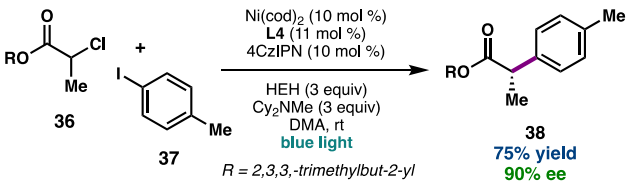
a) Reisman, 2017

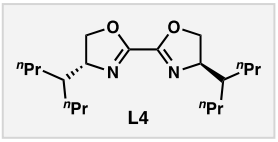


b) Doyle and Sigman, 2017



c) Walsh and Mao, 2020



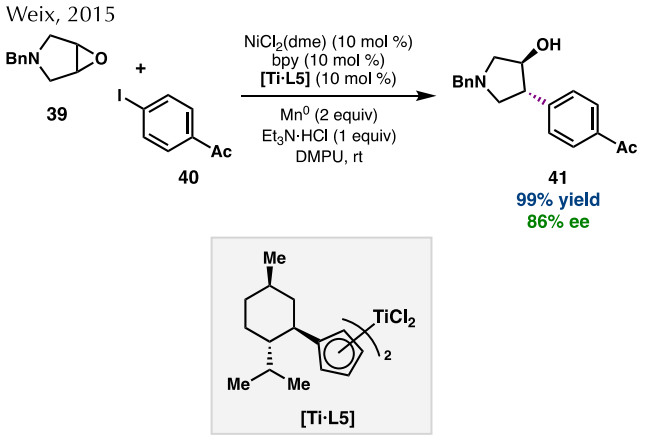


BiOX ligand **L4** has recently enabled the enantioconvergent RCC of α-chloroesters and aryl iodides (**Scheme 7c**).[55] Photoredox catalyst 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) was proposed to turn over the Ni catalyst when Hantzsch ester (HEH) was employed as a soluble terminal reductant. Thus, strategic use of photoredox co-catalysts may preclude the generation of stoichiometric metal waste by Ni-catalyzed reductive cross-couplings.

Expanding the scope of alkyl electrophiles for Ni-catalyzed asymmetric RCC reactions, the Weix group published the enantioselective cross-coupling of

meso-epoxides and aryl halides (**Scheme 8**).[56,57] A chiral titanocene catalyst ([Ti·**L5**]) proposed to generate a β-titanoxy carbon radical from a *meso*-epoxide, which can be intercepted by a Ni(II)–Ar complex arising from an aryl halide. Reductive elimination from the resulting Ni(III) species then gives enantioenriched *trans*-β-arylcycloalkanols in excellent yields. In this transformation, the enantioselectivity is determined in the epoxide-opening step by the chiral titanocene catalyst.[56]

Scheme 8. Enantioconvergent RCC with Ni/Ti co-catalysis.

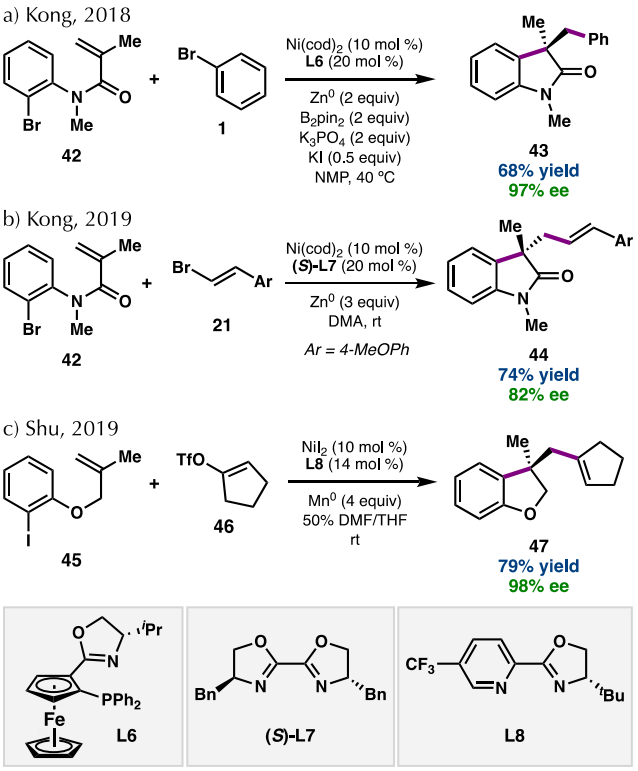


V. Ni-Catalyzed Enantioselective RCC Reactions of Olefins

Recently, olefins have been employed in enantioselective Ni-catalyzed reductive cross-couplings to forge two C–C bonds and a stereogenic center in one reaction. These dicarbofunctionalizations are advantageous in cases where alkyl (pseudo)halide electrophiles are unstable or require multiple steps to prepare, since the C(sp^3) electrophilic fragment is generated directly from an alkene and a C(sp^2) halide. Most of the methods to date involve an initial intramolecular addition of a C(sp^2) electrophile to an alkene. This represents a potential enantiodetermining step that distinguishes these reactions from non-conjunctive RCCs; in-depth mechanistic investigations will be instructive for future reaction development.

In 2018, Kong and coworkers disclosed the enantioselective 1,2-dicarbofunctionalization of activated alkenes to access heterocycles bearing an all-carbon quaternary center (**Scheme 9a**).[58] This 1,2-diarylation required both Zn and B_2pin_2 as terminal reductants, as well as an iodide source (KI) to improve the yield. A phosphinoferrocenyloxazoline ligand (**L6**) induced high levels of enantioselectivity of the products, which featured various arene substitution and tolerance of a few sterically bulky groups at the benzylic position. Similar olefin substrates were found to undergo asymmetric 1,2-arylalkenylation with alkenyl bromide coupling partners (**Scheme 9b**).[59] In this case, chiral BiOX **L7** could be used in the absence of additives to provide oxindoles in good ee.

Scheme 9. Enantioselective RCCs of olefins and C(sp^2) electrophiles.

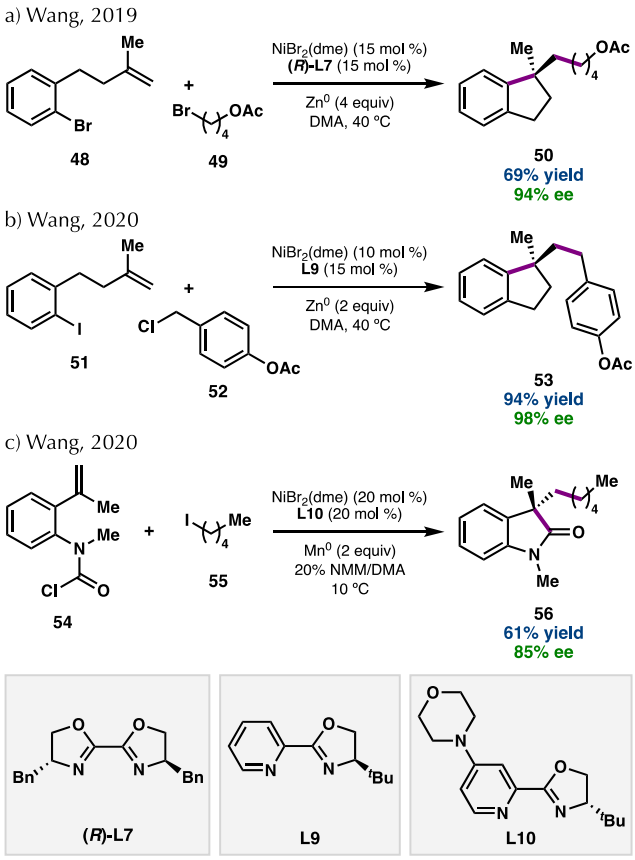


In 2019, Shu and coworkers published a related reductive transformation able to couple unactivated olefins with alkenyl triflates (**Scheme 9c**).[60] Making use of a pyridyloxazoline ligand (PyOx, **L8**), Mn^0 as the stoichiometric reductant, and each electrophile in an equimolar amount, this reaction gives heterocyclic products in moderate to good yield and excellent ee. While this transformation successfully coupled a range of aryl substituents on the alkene partner, only 1,1-disubstitution of the alkene was tolerated.

Key to these processes is the ability of the catalyst to sequentially engage the olefin and cross-coupling partner. In a redox-neutral system, Fu and

coworkers demonstrated that intermediate organonickel species can rapidly undergo olefin insertion to form a five-membered ring that is able to capture an electrophile in an enantioselective fashion.[61] The reductive two-component couplings are thought to proceed via analogous mechanisms.[58,60] Oxidative addition of the aryl halide (**42** or **45**) followed by reduction is proposed to access a Ni(I)–aryl species. This intermediate can undergo migratory insertion of the pendant alkene, which may be the enantiodetermining step. The Ni(I)–alkyl species resulting from this 5-*exo*-trig cyclization is then poised to undergo oxidative addition of the C(sp^2) coupling partner (**1** or **46**) to furnish final product **43** or **47**, respectively, with high levels of enantioselectivity.

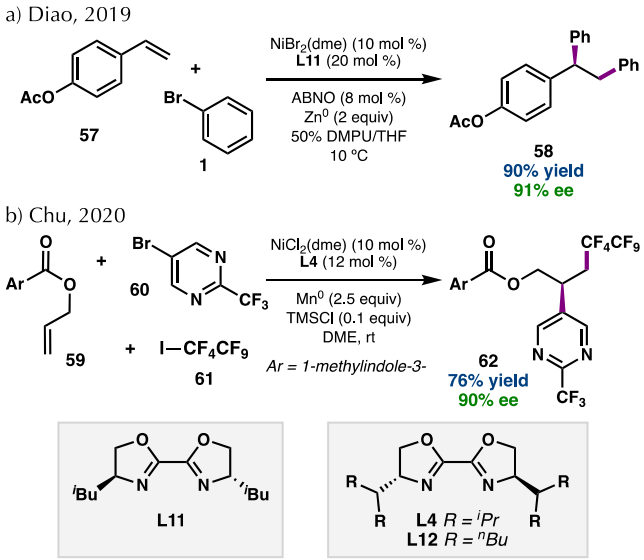
Scheme 10. Enantioselective RCCs of olefins and C(sp^3) electrophiles.



C(sp^3) electrophiles have also shown competence in olefin RCCs. Wang and coworkers reported the reductive 1,2-arylalkylation and 1,2-arylbenzylation of unactivated olefins to form enantioenriched benzene-fused cyclic products (**Scheme 10a,b**).[62] While chiral BiOX ligand **L7** was required for primary bromides,[62a] the coupling of benzylic chlorides was optimal with PyOx **L9**.[62b] These reactions are notable for their ability to form indane products; however, the corresponding tetralins are inaccessible, and tetrahydroisoquinolines were formed with significantly reduced ee, indicating the difficulty of 6-*exo*-trig cyclization. These limitations highlight an opportunity for development to access products featuring other ring sizes.

Soon after, the Wang group demonstrated the ability to couple styrene-tethered acyl chlorides and C(sp^3) electrophiles (**Scheme 10c**).[63] The reaction, which proceeds with Mn^0 as terminal reductant, was found to tolerate groups of varying steric bulk at the benzylic position of **54**. Competent coupling partners included primary and secondary alkyl iodides and benzyl chloride. Although the heterocyclic products were available in moderate to good yields with PyOx **L9**, morpholino-substituted PyOx **L10** was necessary to obtain good levels of enantioselectivity.

Scheme 11. Enantioselective reductive intermolecular cross-coupling of olefins.



In 2019, the Diao group disclosed the first intermolecular enantioselective 1,2-dicarbofunctionalization of activated alkenes, using BiOX **L11** (**Scheme 11a**).[64] Interestingly, catalytic amounts of an *N*-oxyl radical additive (ABNO) enabled the cross-coupling of styrenes and aryl halides to proceed with consistent and high enantioselectivities. Formation of the dibenzyl

homodimer of **57** suggests the presence of an intermediate benzylic radical. In addition, stereochemical results and radical clock experiments support a mechanism involving reversible homolysis of the Ni–alkyl bond resulting from olefin migratory insertion, which may precede enantiodetermining reductive elimination.

In the following year, Chu and coworkers reported the intermolecular reductive coupling of olefins with (hetero)aryl bromides and perfluorinated alkyl iodides (**Scheme 11b**).[65] Use of a pendant directing group facilitated the regiospecific reaction of unactivated alkenes. Chiral BiOX ligands were found to be uniquely effective in this three-component reaction; while previously developed **L4** promoted formation of the 1,2-fluoroalkylarylated products in high yields, extending the alkyl chains of the ligand (**L12**) did not result in enhanced enantioselectivity. This transformation is an important advance from intramolecular olefin RCCs; the difunctionalization of olefins with distinct electrophiles will continue to be an interesting and significant extension of this intermolecular methodology.

VI. Concluding Remarks and Outlook

Efficient C–C bond construction through Ni-catalyzed enantioselective RCC reactions affords valuable enantioenriched small molecules from simple electrophile precursors. We anticipate that addressing several remaining challenges will be required for further advances in the field. The development of new ligand scaffolds will likely be crucial to enhancing the yield and ee of new reactions. Importantly, techniques such as ligand parameterization with multivariate linear regression analysis may draw connections between seemingly scattered data to reveal important trends in reactivity and stereoselectivity. In addition, transitioning away from heterogenous metal reductants may increase industrial use of reductive cross-couplings, as well as facilitate high-throughput screening for development and use of these transformations.

Activated alkyl coupling partners currently dominate the enantioselective RCCs of C(sp^2) and C(sp^3) electrophiles, and several limitations within this category remain. *Ortho*-substituted and *ortho*,*ortho*-disubstituted benzylic electrophiles exhibit low reactivity, as do those featuring sterically bulky α-substituents.[40] The poor stability of electron-rich benzylic halides and α-heteroatom-substituted halides diminishes their utility.[4] Unactivated and tertiary halides remain a significant challenge in enantioselective transformations. Thus, diversifying the pool of competent alkyl (pseudo)halide electrophiles is an important future focus.

To access a broader scope of C(sp^3) coupling partners that can serve as alkyl radical precursors, radical generation mechanisms other than halogen abstraction should be explored. For example, using synergistic photoredox/Ni catalysis for C–H functionalization is an exciting new direction; however, it has been challenging to render these reactions enantioselective.[66,67] Ultimately, the development of new methods of C(sp^3) radical generation will improve the accessibility and synthetic utility of enantioselective RCCs.

Reductive olefin dicarbofunctionalization reactions offer strategic complementarity to the RCC of (pseudo)halide electrophiles. In principle, unactivated olefins can be leveraged to forge stereocenters remote from α-stabilizing groups, which would diverge from the reactivity of activated halides. An advantage of using olefin coupling partners is the ability to access all-carbon quaternary centers, which has yet to be realized in enantioconvergent RCCs. Although current methods are restricted to cyclization of five-membered rings as a strategy to effectively discriminate electrophiles, the recent development of intermolecular olefin RCCs suggests that this is not an intrinsic limitation. Further development of formally three-component couplings will rely on deeper mechanistic understanding to address challenges of electrophile differentiation.

Overall, transition metal-catalyzed cross-coupling reactions remain an invaluable tool for the synthesis of small molecules and natural products. In particular, Ni-catalyzed reductive cross-couplings have enabled the development of mild reaction conditions that give the desired products in good yields with high levels of enantioselectivity. We are confident that this field will continue to grow and

revolutionize the way that carbon–carbon bonds are constructed in an enantioselective manner.

ASSOCIATED CONTENT

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Funding Sources

No competing financial interests have been declared.

ACKNOWLEDGMENT

Fellowship support was provided by the National Science Foundation (graduate research fellowship to K. E. P., S. E. D. Grant No. DGE-1144469). S.E.R. is a Heritage Medical Research Institute Investigator. Financial support from the NIH (R35GM118191-01) is gratefully acknowledged.

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TOC graphic: