Published in final edited form as:

Acc Chem Res. 2018 February 20; 51(2): 567–572. doi:10.1021/acs.accounts.7b00432.

Keeping Track of the Electrons

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Abstract

Mechanistic investigation and new reaction development are intertwined. This interdependence presents challenges and opportunities in development of all transformations, particularly for those that employ base metal catalysts. In comparison to precious metal counterparts, these catalysts yield less easily to mechanistic analysis. However, base metal catalysts can provide new modes of reactivity and opportunities for discovery. In this commentary we highlight a developing field: nickel-catalyzed stereoselective alkyl cross-coupling reactions. While key features of the relevant catalytic cycles remain ambiguous, chemical intuition and key mechanistic experiments have provided the stepping stones for discovery of stereoselective transformations.

Graphical Abstract

I. Introduction

In matters of the intellect, do not pretend that conclusions are certain which are not demonstrated or demonstrable.

—Thomas Huxley, Biologist and Theologist¹

Development of new catalytic reactions is a vigorous and vital part of organic and organometallic chemistry. New transformations await discovery just beyond the horizon, with many new advances within and slightly beyond reach. To develop new transformations,

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different groups take slightly different strategies. All approaches combine phenotypic pattern recognition with potential arrow pushing reaction mechanisms. The mechanisms used as starting points range from well-validated to complete conjecture. In a typical catalytic reaction one or two of the intermediates can be characterized, but the others are fleeting and the arrows are often imagined. Nonetheless, the proposed mechanism serves to guide the experimentalist to envision the next transformation. Even a mechanism that turns out to be invalid can still serve as inspiration to catapult a project forward. We need enough information to make decisions and hypotheses, at the same time recognizing our gaps in knowledge and our assumptions. While chemical intuition can help to identify opportunities, oversimplification can stall progress and prevent transformative breakthroughs. Unlike Monty Python's Sir Bedivere, chemists must avoid the temptation to make leaps based on incorrect assumptions or faulty reasoning. **A holy grail in new reaction development is conducting relevant mechanistic experiments that provide compelling support to define the structures and reactivity of key intermediates, and using this mechanistic evidence to identify new modes of reactivity** (Figure 1).

II. Rising to the challenge: New tools and strategy

There have been major advances in mechanistic evaluation since the "Holy Grails" issue 20 years ago, with new tools being developed and existing techniques sharpened. Traditional methods for kinetic analysis such as NMR and GC continue to be staples.^{2,3} Other methods have been greatly improved, for example, modern reaction calorimetry is significantly more prevalent and straightforward than it was two decades ago.⁴ Additionally, new tools such as measurement of kinetic isotope effects using natural abundance ¹³C have been developed.^{5,6} DFT calculations have been refined and honed to offer improved accuracy for the minute energy differences between competing transition states.^{7,8} To complement mechanistic analysis, strategies for high-throughput evaluation of reaction conditions and product distributions have been developed. These strategies build on the lessons learned from combinatorial chemistry efforts and provide rapid access to new reactivity and highly optimized conditions for a given transformation.^{9,10,11,12} Often high-throughput screens result in identification of a set of reaction conditions, including catalyst precursors, additives, and solvents, that would not have otherwise been predicted by careful analysis of the existing literature. Finally, detailed reaction parameterization is beginning to provide a new physical organic approach to analyze and predict the impact of ligand tuning on catalyst activity and selectivity.^{13,14,15}

III. Case Study: Nickel catalysis of alkyl cross-coupling reactions

As a case study of a field that has been profoundly shaped by mechanistic investigations we examine nickel catalysis of cross-coupling reactions, with a focus on stereoselective cross-coupling reactions of secondary alkyl electrophiles or organometallic reagents. We highlight select examples that illustrate the connections between the proposed reaction mechanisms and rigorous mechanistic investigation to new catalytic advances. Comprehensive reviews provide a full picture of the development of alkyl cross-coupling reactions, including those employing alternative metal catalysts.^{16,17,18}

In 1995, at the time of the first Holy Grails issue, palladium-catalyzed aryl-aryl coupling reactions were poised to take over medicinal chemistry.¹⁹ During the intervening years, aryl cross-coupling has developed into a robust and well-traveled reaction, with participation by designer substrates including heterocycles of all varieties. It has provided access to the chemical space where most new active pharmaceutical agents reside.²⁰ The success of this reaction is due, at least in part, to the reliable and predictable nature of palladium catalysts. Once a typical cross-coupling mechanism was established, these reactions were extrapolated to include a wide range of electrophilic and nucleophilic partners. The palladium catalysts are straightforward to handle and mechanisms are easy to draw on a whiteboard, even for the novice organometallic chemist. While ligand tuning is often required for specialized substrates, most practicing medicinal chemists have access to a sufficient library of the key ligands, so that reactions are nearly guaranteed some measure of success.

In contrast, alkyl coupling, those reactions that employ an alkyl electrophile or alkylmetal reagent or both, was an uncommon transformation in 1995. Proof of concept for these alkyl couplings had been established at that time, but with limited scope and few applications. Unlike aryl-aryl coupling, the field has had a significant induction period, with first reports using nickel catalysts in 1970's,²¹ and advances by Knochel in 1995.^{22,23} The field gained momentum in 2001 when Fu reported the palladium-catalyzed Suzuki coupling of primary alkyl bromides,²⁴ followed by a spring of nickel-catalyzed reactions of secondary substrates that began appearing in 2003.²⁵ Two major factors contributed to the slow maturation of the field. First, the familiar and well-understood palladium complexes are typically not ideal catalysts for cross-coupling reactions with alkyl partners. Nickel complexes more frequently provide access to the desired reactivity, however, these catalysts are not as well-behaved or predictable. Second, in comparison to aryl couplings, alkyl couplings provide a larger array of undesired byproducts. A problematic aryl-aryl Suzuki-Miyaura coupling may provide protodeborylation as the major side product. In contrast, a challenging alkyl coupling can provide mixtures resulting from β -hydride elimination, alkylmetal isomerization, hydrogenolysis, dimerization and unreactive starting materials (Figure 2). We illustrate possible side reactions in the coupling of an alkyl electrophile with an arylmetal reagent. Similar side reactions will occur in reactions employing an alkylmetal reagent and aryl electrophile, or an alkylmetal reagent with an alkyl electrophile. The aggregate challenge of tuning a poorly understood catalyst to shut down a larger number of side reactions likely contributed to the lengthy induction period of the field. Advances after 1995 were bolstered by development of related reactions such as hydroalkylation reactions that proceed through alkylnickel complexes;^{16,17} lessons learned from those projects lowered the barriers, real or perceived, to development of nickel-catalyzed alkyl coupling reactions.

After decades of meticulous experiments from many laboratories, major features of the mechanisms of nickel-catalyzed alkyl cross-couplings are still unrefined and, importantly, likely differ from reaction to reaction. As a base metal complex, a nickel precatalyst can often generate several complexes of varying oxidation states in situ. From a mechanistic perspective, this means that the active catalytic species is frequently non-obvious. Nickel catalysts can also participate in single-electron and two-electron reactions,^{26,27} in contrast to the precious metal catalysts that typically favor two-electron reactions. Therefore, while there is robust mechanistic evidence that palladium-catalyzed cross-coupling reactions

proceed through Pd(0) and Pd(II) intermediates, the oxidation states of key intermediates in nickel-catalyzed cross-coupling reactions are still ambiguous. At first glance, based on analogy to palladium and the oxidation state of catalyst precursors, one might assume that Ni(0) and Ni(II) intermediates are most likely. However, in seminal studies in the 1970's, Kochi and co-workers established that reductive elimination likely occurs from Ni(III) intermediates, and not from Ni(II) complexes (Scheme 1a).^{28,29} Kumada and co-workers incorporated these data into the proposed mechanism for coupling of Grignard reagents with alkyl halides, illustrating established intermediates and avoiding proposed structures for intermediates that lack structural characterization (Scheme 1b).³⁰ Additional experiments have subsequently been reported that also implicate Ni(III) intermediates and, by extrapolation, Ni(I) intermediates.^{31,32,33} In general, further studies to pin down key intermediates have been hampered by the instability of the intermediates themselves, particularly with catalytically relevant ligands, and rapid redox cycling of nickel complexes in solution. For example, Ni(II) complexes have been isolated, however, whether or not they are true catalytic intermediates or simply catalyst precursors is not always straightforward to determine. Extrapolation from rigorous mechanistic studies to complex cycles must be tentative. The exact identity of the ligand will play a critical role and may alter the mechanisms, for example, in comparisons between catalysts supported by redox-active and redox-innocent ligands.³² The identity of the oxidative addition partners will also impact the mechanism. For example, DFT calculations of aryl-aryl and alkyl-aryl coupling reactions of carbamates are consistent with Ni(0)-Ni(II) catalytic cycles.^{34,35} These results are consistent with the mechanisms proposed for allylic substitution reactions of ethers.^{36,37} Current approaches must balance a desire to simplify and rationalize the observed reactivity with the knowledge that little data supports the proposed mechanisms.

Despite the fact that many key features of the catalytic cycles are incomplete, mechanistic studies have been critical in guiding the development of new alkyl coupling reactions. For example, inspired by Kochi's evidence that oxidation of Ni(II) intermediates facilitates reductive elimination, Knochel and co-workers reported that otherwise sluggish cross-couplings could be accelerated by pendant alkenes and alkynes or additives such as electron-deficient alkenes.^{22,23} The mechanistic hypothesis that there are likely alkyl radicals formed during oxidative addition of alkyl halides with low-valent nickel complexes lead to the Fu laboratory's discovery that chiral ligands could influence a stereoablative and stereoconvergent transformation. These examples underscore the importance of rigorous mechanistic experiments. While we may never have complete answers, we may learn enough to move forward to new discoveries.

With the viability of nickel-catalyzed alkyl cross-coupling reactions established, the field has gained momentum and is currently developing rapidly. Cross-coupling of primary substrates has begun to be adopted in synthesis, now that reasonably general catalysts and reaction conditions have been identified.³⁸ The implementation of secondary substrates in these reactions provides the opportunity to generate new stereogenic centers with control of absolute configuration and is currently an area of rapid development. Both stereoconvergent and stereospecific alkyl cross-couplings have been established, using secondary electrophiles and organometallic reagents.^{17,18} Representative examples are shown in Scheme 2. Stereoconvergent reactions of racemic alkyl halides employ chiral catalysts and rely on the

formation of alkyl radical intermediates during the course of the cross-coupling reaction, either during the oxidative addition event or by equilibration of diastereomeric alkylmetal intermediates (Scheme 2a).^{39,40,41} Stereospecific reactions require enantioenriched starting materials and mechanisms which avoid alkyl radical intermediates. Stereospecific reactions of alkyl ethers and esters have been established (Scheme 2b).^{42,43} Stereospecific reactions of chiral transmetallating agents, including alkylboranes⁴⁴ and alkylstannatranes⁴⁵ build on early reports which demonstrated that transmetalation is typically highly stereospecific (Scheme 2c).^{16,46} Stereoconvergent reactions of racemic alkylmetal reagents are the least well-developed reactions, although proof of concept was established using Grignard reagents in the 1980's (Scheme 2d).⁴⁷ The scope of each of these transformations continues to expand and push beyond expected limitations. For example, stereospecific reactions of tertiary esters provide access to enantioenriched quaternary carbon centers.⁴⁸ Creative strategies to enter the catalytic cycle invigorate the field, including employing photocatalytic conditions for formation of alkylradical intermediates.^{49,50,51}

Branching away from robust aryl-aryl cross-coupling reactions to explore the unknown territory of alkyl cross-couplings is providing powerful new approaches for stereoselective C–C bond formation. Many challenges and questions remain to be addressed. Will this reaction ever be truly general? Will it be embraced by medicinal chemistry in the same way that aryl cross-couplings have? How much more will we learn about the mechanisms? Development of these reactions has already begun to have long-range impacts on related transformations, for example, in providing the framework for control of stereochemistry in cross-electrophile coupling reactions.^{52,53,54,55}

IV. Outlook

For a research worker, the unforgotten moments of life are those rare ones, which come after years of plodding work, when the veil over nature's secret seems suddenly to lift and when what was dark and chaotic appears in a clear and beautiful light and pattern.

—Gerty Cori, Nobel Laureate 1947⁵⁶

Development of new catalytic reactions flourishes in the intersection of organometallic and physical organic chemistry. Nickel-catalyzed alkyl cross-coupling reactions provide examples of how chemists employ hard-won and sometimes ambiguous mechanistic data to guide discovery of new transformations. As the field of physical organic chemistry continues to evolve, new experimental methods will provide increased resolution for challenging mechanisms. Continued growth and improved fundamental understanding of transition metal complexes, including base metal catalysts, will provide access to new modes of reactivity with yet-undiscovered applications in organic synthesis. The next transformative advances will continue to be driven by the curiosity of chemists who want to better understand their reactions.

ACKNOWLEDGMENT

This work was supported by NIH NIGMS (R01GM100212). Tiffany Chin is acknowledged for conspectus artwork and Figure 1.

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Figure 1:
Experiments that capture mechanistic details can drive the logical development of new reactions.

(a) Typical aryl-aryl cross-coupling reaction

(b) Typical alkyl-aryl cross-coupling reaction

Figure 2:

Aryl-aryl coupling vs. alkyl-aryl coupling. (a) Aryl-aryl cross-coupling typically employs a palladium catalyst and provides excellent yields of the desired product and minimal undesired reactivity. (b) Alkyl-aryl cross-coupling typically requires a nickel catalyst and can be more challenging due to the host of possible byproducts. The illustrated example employs an alkyl electrophile; similar side reactions occur in reactions employing alkylmetal reagents.

(a) Kochi 1975, 1979

(b) Kumada 1976

Scheme 1:

Pioneering studies of the mechanism of nickel-catalyzed cross-couplings. (a) Kochi's experiments demonstrated that in nickel-catalyzed cross-coupling reactions a Ni(III) intermediate likely undergoes reductive elimination to generate the product. (b) The catalytic cycle drawn by Kumada provides sufficient detail to understand the pathway for the nickel-catalyzed cross-coupling reaction and focuses on intermediates for which there is experimental evidence.

(a) Stereoconvergent cross-coupling of racemic electrophiles

(b) Stereospecific cross-coupling of enantioenriched electrophiles

(c) Stereospecific reaction of chiral transmetallating agents

(d) Stereoconvergent reaction of racemic transmetallating agents

Scheme 2:

Representative enantioselective alkyl cross-coupling reactions. (a) Stereoconvergent cross-coupling reactions of racemic alkyl bromides with alkylboron reagents. (b) Stereospecific cross-coupling reactions of enantioenriched alkyl ethers with Grignard reagents. (c) Stereospecific reactions of enantioenriched alkylboranes with aryl iodides. (d) Stereoconvergent reactions of racemic Grignard reagents with vinyl bromides.