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Multimetallic-Catalyzed C—C Bond-Forming Reactions: From Serendipity to Strategy

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Abstract

The use of two or more metal catalysts in a reaction is a powerful synthetic strategy to access complex targets efficiently and selectively from simple starting materials. While capable of uniting distinct reactivities, the principles governing multimetallic catalysis are not always intuitive, making the discovery and optimization of new reactions challenging. Here, we outline our perspective on the design elements of multimetallic catalysis using precedent from well-documented C—C bond forming reactions. These strategies provide insight into the synergy of metal catalysts and compatibility of the individual components of a reaction. Advantages and limitations are discussed to promote further development of the field.

Graphical Abstract

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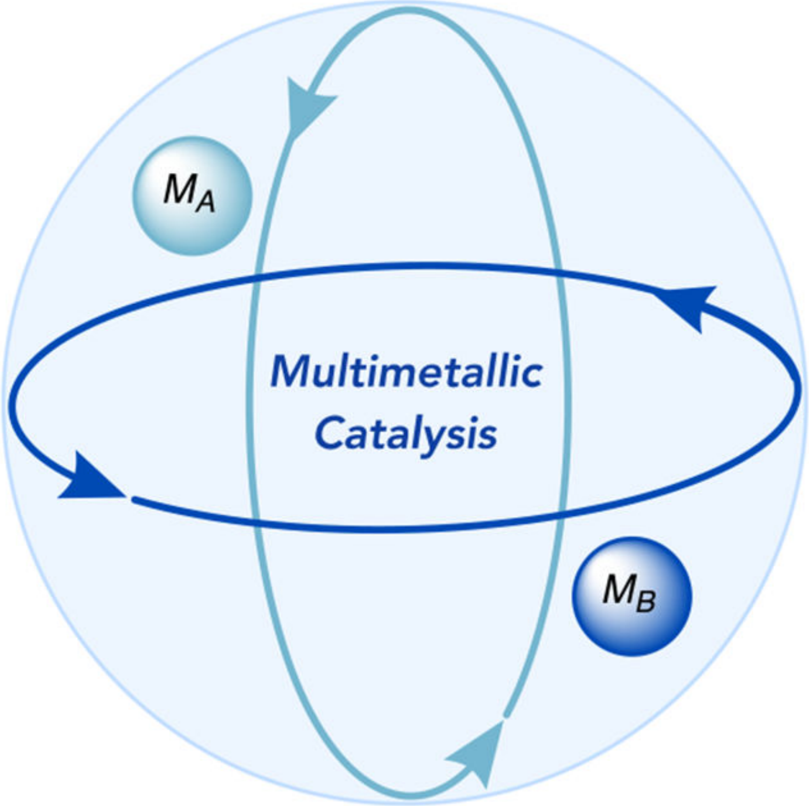

INTRODUCTION

Transition metal catalysis plays a central role in organic synthesis, from small-scale medicinal chemistry to multi-ton scale polymer chemistry. The power of transition-metal catalysis allows chemists to tune a single catalyst to favor difficult bond-breaking and bond-forming steps. However, a single metal catalyst can be limiting when reaction steps of a transformation have competing requirements, such as oxidative addition and reductive elimination (Figure 1A). A solution to these cases is multimetallic catalysis (Figure 1B), a process in which two or more metal catalysts work in concert to enable a single synthetic transformation.[1-8] This catalytic strategy is distinct from orthogonal tandem catalysis, when *sequential,* independent reactions occur in the same flask, each catalyzed by a single catalyst.[9-11] In a multimetallic system both metals operate simultaneously, rather than sequentially: both metals are necessary for catalytic turnover. Reactions can be distinguished by how the two metals interact (Figure 1B). Accordingly, multimetallic catalysis can provide advantages beyond what a single metal catalyst can achieve by enhancing reactivity and selectivity, avoiding the need for stoichiometric metals, and/or enabling new chemistry. Although there are many historical examples of multiple metals being used in concert to promote reactivity, it is only within the last several decades that gains in our fundamental understanding of single-metal organometallic-chemistry have rendered the *design* of multimetallic catalysis accessible. Early multimetallic catalyzed reactions were discovered serendipitously, with many methods arising from the use of metal salt additives to improve known transition metal-catalyzed reactions.[12] In recent years, the development of C—C bond forming methodologies paved the way for considering how two metals might operate together to activate a substrate, transfer a reactive group, or facilitate challenging bond formations. These studies, while focused on multimetallic catalysis for C—C bond formation, can provide insight for a broader expanse of synthetic chemistry. This perspective therefore focuses on the *design principles* of multimetallic catalysis, summarizing lessons that can be gleaned from prior art and suggesting areas where further studies are needed. We will discuss key design principles for catalyst selection, factors that govern selectivity (e.g., cross-selectivity and stereoselectivity), and considerations for success within five main mechanistic classes (redox activation, substrate activation and capture, domino multimetallic reactions, transmetalation, and shuttle).

DESIGN PRINCIPLES OF MULTIMETALLIC CATALYSIS

Recent advances in multimetallic-catalyzed reactions for C—C bond formation reveal principles that can be adopted in the design of new reactions. Key considerations in devising multimetallic systems are: 1) choosing what metals to pair together; 2) favoring cross-reactivity between catalysts to outcompete or prevent self-reactivity by one of the catalysts; and 3) optimizing more complex systems that contain multiple metals and multiple ligands.

Metal Catalyst Selection in Multimetallic Catalysis

A common approach to multimetallic catalytic systems for C—C bond formation combines metal catalysts with complementary reactivity (Figure 2A). When a single metal catalyst can selectively activate one substrate, there is opportunity for a second metal catalyst to enable reactivity that would not have been possible with the first catalyst alone. However, choosing effective pairings of metal catalysts is not always straightforward. The most extreme case is redox incompatibility – for example, one metal may cause the plating out of the other metal, rendering the latter catalyst no longer reactive in a synthetic transformation.[13] Alternatively, catalyst deactivation by over-ligation or deleterious speciation in systems with multiple metals and ligands can be limiting (*vide infra*). More complicated are the intermediate cases, when unanticipated, reactive off-cycle species participate in side reactions.

To avoid these limitations, successful C—C bond forming strategies can guide the examination of effective metal pairings. As intrinsic properties of metals vary across the periodic table, pairing early and late transition metals, as well as pairing metals across the first, second, and third rows, have proven effective at promoting unique transformations. A common strategy in the recent literature is to employ group 11 metals (Cu, Ag, Au) with group 10 metals (most commonly Pd or Ni). A historic example of this type of reaction is the Sonogashira reaction (Scheme 1).[14] In this reaction a Cu salt reacts efficiently with π systems such as alkynes to form copper acetylide intermediates. The complementary coupling partner, an organo(pseudo)halide, remains untouched by Cu, enabling reactivity when paired with a group 10 metal (Pd). Together, Cu and Pd catalysis allow for the formation of a new C—C bond without one catalyst interfering with the other's activity.

Increasingly, radical-generating catalysts (Co, Ti, Fe) and photoredox catalysts (Ir, Ru) have been employed in systems with metals associated with cross-coupling (Ni, Pd, or Cu) (Figure 2A). Ni, Pd, and Cu, while affording short excited-state lifetimes upon irradiation, are efficient at radical capture to form a stabilized intermediate. These metals are also effective at capturing radicals under thermal conditions. In the process of trapping radical species, the oxidation state of the metal is increased, thereby forming a complex that will facilitate the bond-forming step. Reductive elimination from these higher-valent intermediates serves as a powerful method for forming new C—X and C—C bonds.[15] In some cases, these new radical pathways can be an improvement over established steps from monometallic systems (such as a replacement for transmetalation) or they can unlock new reactivity (as in hydrogen-atom transfer steps).

Other common combinations of catalysts also leverage complementary reactivity differences (Figure 2A). In the Nozaki-Hiyama-Kishi (NHK) reaction, the metal that activates the organic halide (Ni or Co) can be paired with a more oxophilic metal (Cr) for migratory insertion into the polarized C=O bond of the second substrate (Scheme 2). In π-allyl chemistry, Pd can generate an electrophilic metal intermediate that reacts with a nucleophile generated by Au or Rh (*vide infra*).[16,17] While many metal combinations rely on early/late metal pairings to guide catalysis, it has also proven fruitful to pair first row metals with second or third row metals: reactions that pair 3d (Co, Ni, Cu) with 5d (Ir, for metallaphotoredox catalysis) or 4d (Pd) metals are now well established.

Additionally, we have found that within a group, 3d (Ni) and 4d (Pd) metals can complement each other due to their different atomic sizes, electronegativities, and preferred oxidation states.[18-20] While not as common in small molecule synthesis, combinations of two early metals (with a third shuttling catalyst) have proven successful at-scale for polymer synthesis (*vide infra*).[21]

Ligand Choice Considerations in Multimetallic Catalysis

Ligand selection is a critical parameter in the development of multimetallic-catalyzed reactions (Figure 2C). Consistent with monometallic processes, the ligands employed in a multimetallic reaction will modify the reactivity and selectivity of each catalyst. Just as metal catalysts are paired together to facilitate distinct steps in a reaction, the ligands that tune them are frequently distinct as well and can be essential for promoting desired reactivity. Anticipated issues with using distinct ligands with paired metal catalysts in reactions include: 1) negative ligand-metal interactions leading to catalyst decomposition, 2) catalyst deactivation from one metal taking both ligands, and 3) the formation of catalysts with undesired reactivity.

Despite these challenges, ligand selection in multimetallic reactions does have additional flexibility compared to monometallic reactions. Because individual catalysts in multimetallic reactions do not need to conduct all elementary steps in a reaction, it is possible to use ligands that strongly bias a catalyst for a single step. For example, an electron-rich, unhindered ligand supports oxidative addition, but would not favor reductive elimination (an electron-deficient and sterically hindered ligand would be best for achieving the latter step). Moreover, if a catalyst is required to favor single-electron and atom-transfer events, higher coordinate ligands (coordination number of 3-5) will be amenable to these transformations, but would slow polar, inner-sphere events.

While distinct ligand classes are frequently chosen for different metals, it is not a pre-requisite. For example, many Ni and Ir photoredox reactions utilize analogous or even identical bipyridine ligands on both metal catalysts, limiting issues with ligand exchange. Ultimately, desirable ligands for multimetallic reactions should be easily modified for reaction optimization and have minimal negative interactions with other compounds (e.g., solvent, substrate, product, and the other catalyst).[10,22,23] Even in monometallic reactions, multiple ligand-metal complexes can be formed *in situ* (e.g. $(Ph_3P)_2Pd$, $(Ph_3P)_3Pd$ in cross-couplings reactions). In multimetallic catalytic reactions, speciation can be more complex if multiple different ligands are present.

In cases when ligand exchange is slow compared to the desired chemistry, pre-ligated precatalysts can be employed advantageously. Pre-formed cobalt phthalocyanine (Co(Pc)) does not suffer from ligand exchange (for example, in a reaction involving Ni or Cr co-catalysts) because metal phthalocyanines are slow to transmetalate.[24-26] This strategy is most often useful when one catalyst utilizes a multidentate ligand with a strong ligand field, such as phthalocyanine, porphyrin, or cyclopentadienyl ligands.

When ligand exchange between the two catalysts is fast, ligand “self-sorting” can maintain the required metal-ligand pairings in multimetallic processes. Hard-soft acid base (HSAB) theory provides guidelines for selecting ligands that will preferentially bind to one metal ion over another (e.g., softer phosphines prefer late 2nd and 3rd row metals).[27] The area of metal ion sensing offers additional guidance for selective ligation: enormous differences in association constants have been observed even between metals that have similar diameters.[28,29] Selectivity can be derived from a variety of factors, such as preferred geometry.[30-32] For example, selective ligation of linked sulfonamide-oxazoline and phenanthroline ligands with Cr and Ni was demonstrated by Kishi for applications in asymmetric NHK reactions.[33]

In the development of new multimetallic catalytic reactions, effective ligand pairings do not necessarily require selective ligation. When ligand cross-over is inevitable and ligand self-sorting is poorly selective, optimal ligand pairs are those in which the mis-matched catalytic species have low activity, thereby behaving as off-cycle reservoirs of metal and ligand. This is consistent with monometallic systems when ML_0, ML_1, and ML_2 species are all formed, but only one of these catalysts is responsible for the majority of productive chemistry.[34-36] A successful example of this type of ligand pairing surfaced when studying Ni- and Pd-catalyzed cross-coupling reactions. In Ni and Pd systems with bisphosphine and bipyridine ligands (Figure 2C; mechanism shown in Scheme 14), we discovered that while the desired reactivity for cross-coupling occurred with a Ni/bipyridine and Pd/bisphosphine combination, the reverse combinations (Ni/bisphosphine and Pd/bipyridine) gave negligible competitive reactivity.[18,19] Taken together, multimetallic reactions can proceed in high yield even in cases when ligand exchange is a possibility between two metals.

Achieving Cross-Selectivity in Multimetallic Catalytic Reactions

In many multimetallic reactions, substrate dimerization (homocoupling) can compete with the desired transformation. Selective cross-product formation requires that group transfer between the two different catalysts is favored over group transfer between two of the same catalyst (Figure 2B). An instructive model for this process can be derived from monometallic Pd-catalyzed cross-coupling reactions of pre-formed organometallic reagents (e.g., Ar—ZnBr) with an organic electrophile (e.g., Ar—Br) (Scheme 3). The pre-formed organozinc reagent is present in high concentration compared to any palladium intermediates and, although Zn/Zn exchange is possible, Zn is incapable of forming biaryls (cross-products or homocoupling products). The arylpalladium intermediate formed from oxidative addition is present in low concentration. Due in part to this difference in concentration, the arylpalladium species is slower to form homodimeric products by self-exchange than it is to form cross-products from transmetalation with the arylzinc reagent. These concepts can be extended to multimetallic catalysis: the combination of a catalytically-generated, stable group 11 organometallic intermediate with another metal that is slow to form dimeric products (e.g., Pd) has proven to be a general and useful strategy.[3] In practice, however, many catalytic metal intermediates are prone to self-reactivity and alternative design strategies must be considered.

A second guiding principle for the design of cross-selectivity in multimetallic catalytic reactions is a metal analog of the persistent radical effect,[37] referred to herein as the *persistent metal effect*.[18] In the persistent radical effect, cross-selectivity is achieved via differences in the relative concentrations of intermediates tied to small differences in self- and cross-reactivity (Figure 2B). Recent insightful discussions of the persistent radical effect by Leifert and Studer can be generalized to explain when the persistent metal effect will operate:[38] both active metal intermediates should be generated at about equal rates, and one metal should be slow to react with itself.

While, at first, this consideration of persistent metal intermediates appears to add complexity to the design of a method, in practice it greatly increases the pool of potential catalysts that can be applied in a system. Catalyst systems can be employed together selectively even if one or both of the catalysts can form dimeric products. Provided that one metal forms dimer faster than the other, a build-up in concentration of one relatively stable metal intermediate in a reaction can selectively react with a relatively unstable metal intermediate. The unintuitive conclusion is that a fast, unselective catalyst can be a good component of a cross-selective multimetallic system. Within this manifold, Ni/Pd multimetallic catalysis has proven fruitful for achieving cross-selectivity despite Ni catalysts' propensity toward dimerization (Figure 7 and Scheme 14). Due to the importance of the relative rates in the combined catalyst system, the best parameters for the optimization of a single metal catalyst are not always applicable to a dual metal-catalyzed system. This opens new avenues for the (re)exploration of mild reagents, additives, and solvents which may have proven unsuccessful in previous monometallic systems.

The persistent metal/radical effect also underlies the robust nature of systems that utilize alkyl radical intermediates to transfer groups between catalysts. If the radical-intercepting catalyst is slower to self-react than it is to react with the radical, cross-selectivity in a coupling reaction can be high. It has also been noted that, in net redox-neutral reactions of this type, electron transfer between the two catalysts is required for turnover. In these instances, the rates of radical generation and consumption are linked.[39-41]

We have recently found that group transfer in multimetallic systems can be mediated by a third metal, a species that serves as a shuttle between the two catalysts (discussed in detail at Figure 8).[19,42] While zinc chain-shuttling co-catalysis has been studied in polymerization chemistry[21] the potential for its use outside of polymer synthesis has not been broadly exploited. The ability to form a reservoir of non-self-reactive intermediates, such as organozinc reagents, offers new approaches to control selectivity and increase molecular complexity.[43]

Achieving Stereoselectivity in Multimetallic Catalytic Reactions

Stereoselectivity can be challenging to achieve in monometallic catalytic transformations because the same catalyst is required to enable high stereoselectivity for a single step while remaining efficient for all of the other steps in catalysis. The same conditions that afford high enantio- or diastereoselectivity frequently result in poor product yields in monometallic reactions. Ensuring that both selectivity and reactivity are addressed with a single metal-ligand pairing requires an extensive optimization process. Asymmetric multimetallic reactions possess a strategic advantage compared to monometallic reactions due to the possibility of independently optimizing reactivity with one catalyst and selectivity with another. Generally, the design of asymmetric multimetallic catalytic reactions relies upon two strategies (Figure 3A): one strategy which requires only a single metal catalyst to induce chirality, and a second strategy when two chiral catalysts must interact to achieve the desired stereochemical outcome in a reaction.

The first asymmetric strategy is exemplified by cooperativity between Cu and Pd (Figure 3B). Building on carboboration work from Semba/Nakao,[44] Brown,[45,46] and Liao,[47] Buchwald reported an enantioselective Cu/Pd-catalyzed hydroarylation of styrenes in 2016.[48] In this work, a chiral Cu (*R*)-DTBM-SEGPHOS catalyst was employed with an achiral (BrettPhos)Pd catalyst. The mechanism proceeded via the generation of a chiral CuH catalyst that reacted with styrene though a stereoselective hydrocupration (Figure 3B). Simultaneously, the Pd catalyst activated an aryl bromide, generating a Pd(II) aryl halide intermediate. Enantioenriched 1,1-diarylalkanes were formed via a stereospecific transmetalation from Cu(I) to Pd(II). Notably, Buchwald's methodology demonstrated that it is possible, even in a stereoselective reaction, to use Pd and Cu salts after pre-stirring them with their intended ligands, and still maintain high stereoselectivity.

Reductive nickel-catalyzed cross-electrophile coupling reactions also demonstrate the modularity of multimetallic stereocontrol. These reactions generally proceed via a radical-polar mechanism: the Ni catalyst is responsible for oxidative addition of an electrophile, radical capture, and bond formation; a second metal catalyst facilitates radical generation from a variety of precursors. In these systems, a chiral ligand can be placed on either the bond-forming Ni catalyst or the radical-generating catalyst.

In the enantioselective cross-coupling of *meso*-epoxides with aryl halides, the enantiodetermining step is the Ti-mediated single electron ring opening of the epoxide to form a scalemic alcohol containing an adjacent carbon radical (*vide infra,* Figure 5B).[49] The enantioselectivity of the system is controlled by a chiral, menthol-derived titanium catalyst, while the nickel catalyst is achiral. The system forms *trans* products due to the nickel catalyst capturing the radical from the less-hindered face, opposite the site of Ti binding. Several other multimetallic systems utilize a similar Ti-based desymmetrization approach (e.g., Co/Ti).[50]

When the enantiodetermining step is reductive elimination, the chiral ligand is placed on the bond-forming metal. For example, in the Co/Ni-catalyzed coupling of α-silyl benzylic radicals with vinyl halides to form scalemic allyl silanes, the Co phthalocyanine catalyst generates the radical from racemic starting materials[51,52] and a chiral nickel catalyst forms the bond and sets the stereochemistry (Scheme 4).[53] Computational studies on related systems suggest that radical capture is reversible and reductive elimination is stereodetermining.[54,55]

A final example of how two metal catalysts can be independently optimized, one for stereoselectivity and one for yield, is Yoon's enantioselective [2+2] photocycloaddition of 2'-hydroxychalcones (Scheme 5).[56] In this reaction a Lewis acid, (Sc(III)*(S,S)*-*t*-Bu-PyBox) coordinates with the 2'-hydroxychalcone substrate. This coordination lowers the triplet energy of the substrate enone (S_0-T_1 gap is 33 kcal/mol), facilitating energy transfer via an excited Ru photosensitizer ($Ru(bpy)_3(PF_6)_2$) and promotes a stepwise cycloaddition. While use of the photosensitizer alone can lead to a [4+2] Diels-Alder reaction, only [2+2] chemistry is observed in the bimetallic Ru/Sc reaction. Moreover, due to an endergonic triplet energy transfer without Lewis Acid complexation (S_0-T_1 gap is 54 kcal/mol), there is no racemic background for this reaction. By relying on the Lewis Acid to provide chiral induction, no alteration of the photosensitizer is necessary that could otherwise adversely alter its photophysical properties.

The second type of stereoselective multimetallic strategy can provide opportunities for stereoinduction via the pairing of two chiral metal catalysts acting on a substrate simultaneously. Jacobsen and coworkers have developed multiple asymmetric epoxide ring-opening reactions using bimetallic catalysis.[57] In a C—C bond-forming implementation of this strategy, $(pybox)YbCl_3$ catalyzed the addition of TMSCN to *meso* epoxides to form β-trimethylsilyloxy nitrile products (83-92% *ee*). The mechanistic proposal involved the cooperation of a Lewis acidic (pybox)ytterbium species to activate the epoxide and a (pybox)cyanoytterbium species to deliver nucleophilic cyanide (Figure 3B).[58]

Another example of two chiral catalysts synergistically affording stereoselectivity is the Cu/Ir-catalyzed α-allylation of α-heteroaryl amides (Figure 3C).[59] The copper Walphos catalyst controlled the stereocenter α to the amide by chelation to the amide and heterocycle while the iridium phosphoramidite catalyst set the allylic stereocenter β to the amide via an iridium π-allyl intermediate. Reaction of the copper enolate intermediate with the iridium π-allyl intermediate afforded C—C bond formation and set two stereocenters. Both catalysts operated independently for stereocontrol. By mixing and matching the two chiral catalysts this method allows access to all four possible stereoisomers in high *ee* and dr (up to >99% *ee* and >20:1 dr).

When two catalysts come together to form a single, stereodefining transition state, limiting the potential coordination sites on the two catalysts can be paramount. Furthermore, loss of a *chiral* ligand on the enantioselectivity determining metal, or having multiple pathways to form product, could result in poor stereocontrol. To overcome this possibility, catalysts in enantioselective multimetallic reactions often contain chelating ligands or use the same chiral ligand for both catalysts. In the aforementioned epoxide reactions reported by Jacobsen and coworkers, reactivity can take place at the axial positions of a metal catalyst through the d_{z^2} orbital, but cannot occur at equatorial sites as these sites are occupied by a tridentate or tetradentate ligand.[57,58] This limits reactivity to a single type of binding site. Similarly, the π-allyl iridium intermediate has a chiral cleft that provides high enantioselectivities regardless of the nucleophile, and because the ligand is cyclometalated onto Ir, ligand exchange is slow.[59] Therefore, the copper catalyst could be optimized independently of the Ir catalyst and ligand exchange was prevented.

CLASSIFICATION OF MULTIMETALLIC CATALYSIS

Multimetallic reactions can be classified by the role the two metals play in enabling a successful reaction. Herein we describe five types of mechanistic pathways, defined by how the metals interact with each other:

- *redox activation*, when one metal transfers electron(s) (or energy) to and from a second metal
- *activation and capture*, when a single metal reacts with a substrate to form a non-metallic, reactive intermediate, such as a radical, that another metal can trap for functionalization
- *domino multimetallic reaction*, when one of the catalysts sequentially activates and rearranges a substrate before reaction/transfer with the second catalyst
- *transmetalation*, when each catalyst activates a distinct substrate, followed by a group transfer event between the metals
- *shuttle*, when a third metal transfers a substrate from one metal to another metal.

In each of these reaction categories the metal catalysts perform independent roles that are connected via electron, group, or substrate transfer.

Redox Activation

Multimetallic catalysis has proven to be an important tool for modulating the redox state of a metal catalyst (Figure 4A). This process can be part of an electron-transfer chain for a net oxidative or reductive reaction (Figure 4B). Alternatively, a transient redox event can facilitate individual steps and/or close a catalytic cycle in a redox-neutral reaction (Figure 4C). For the purposes of discussion, we also include energy transfer reactions within this classification, despite the lack of a redox event.

A classical example of the redox chain is the Wacker-Tsuji oxidation of olefins, a process catalyzed by Pd and Cu, for the preparation of carbonyl products (Figure 4B). Without the proper ligands on Pd, dioxygen can be slow to oxidize Pd(0) to Pd(II) directly.[60,61] For this reason, Cu and Pd have been employed rather than Pd alone. Cu(I) is easily oxidized to Cu(II) by dioxygen, and Cu(II) can oxidize Pd(0) to Pd(II).[62] The Wacker oxidation demonstrates the power of multimetallic catalysis via redox activation in an important industrial process: while Cu does not engage directly with either substrate in the reaction (alkene or water), its role is critical for the efficient synthesis of carbonyl products.

Photoredox catalysts can also be used to enable catalyst turnover.[63,64] Ni-catalyzed reductive cross-electrophile coupling of aryl halides with alkyl halides is most commonly turned over with stoichiometric metallic reductants (e.g., Zn, Mn),[65] but these reagents can present problems related to stirring and waste disposal. Alternatively, simple amines, which might be envisioned to act as sacrificial electron donors, are not sufficiently potent reductants to reduce Ni(II or I) back to Ni(0) to close a catalytic cycle after a bond-forming step. A photoredox catalyst can overcome this limitation by harnessing the energy available in visible-light photons (Scheme 6).[66] Upon excitation by visible light, a photoredox catalyst can generate a long-lived excited state that can serve as a single electron reductant or oxidant. Therefore, while ground-state Ir(III) cannot be reduced by the amine, photoexcited *Ir(III) can be reduced by the amine, resulting in the formation of an Ir(II) species (reduction) and the corresponding amine radical cation (oxidation). The Ir(II) photoredox catalyst now possesses sufficient reducing power to convert Ni(I) to Ni(0) for catalytic turnover (for example, $[Ir[dF(CF_3)ppy]_2(dtbbpy)]PF_6$ $E_{1/2} = -1.37$ V vs SCE in MeCN; (dtbbpy)Ni(I) $E_p = -1.17$ V vs SCE in THF).[67] In this way, a simple amine, a photocatalyst, and visible light can replace stoichiometric metal reductants.

Besides assisting in catalyst reduction for turnover (Scheme 6), redox catalysts can also enable challenging elementary steps, such as reductive elimination, in otherwise redox-neutral catalytic reactions. It has long been noted that stoichiometric oxidants or electrochemical oxidation could induce reductive elimination in cases when thermal activation failed,[68,69] but these reagents are often incompatible with other steps in catalytic cycles. In place of stoichiometric oxidants, photoredox catalysis has proven general at enhancing the rate of challenging reductive elimination steps by transient oxidation. In a Ni-catalyzed coupling between aryl bromides and alcohols to form ethers, the MacMillan group noted that the C—O reductive elimination step was endergonic from Ni(II), but oxidation to Ni(III) by an excited state Ir photoredox catalyst could render the step favorable (Figure 4C).[70] To close the redox cycle, the Ni(I) intermediate formed after reductive elimination was proposed to undergo reduction to Ni(0) by the reduced Ir(II) photocatalyst, thereby regenerating both metal catalysts. A number of related challenging transformations have been reported under Ir/Ni/$h\nu$ conditions. While the mechanism of action has been debated and may differ between different conditions (e.g., oxidation, energy transfer, rescuing off-cycle intermediates),[71-76] these processes are all clearly multimetallic in nature.

Generally, metals with higher oxidation states enable faster rates of reductive elimination, while metals with lower oxidation states facilitate oxidative addition, but oxidation state manipulations can also unlock new reactivity. For example, a classical synthetic application of halogen radical generation is free-radical halogenation of alkanes. Utilizing a multimetallic (Ni/Ir) strategy, the Doyle lab recently reported several valuable free-radical C—C bond-forming reactions (Scheme 7).[67,77,78] The key to these processes is the generation of alkyl radicals by Cl• in the presence of organonickel(II) intermediates that can intercept and couple alkyl radicals as they are formed.[72] The transient Cl• is formed by photo-induced homolysis of Ni—Cl bonds in arylnickel(III) chloride intermediates, which are in turn generated by *Ir(III)-mediated oxidation of the resting-state arylnickel(II) chloride species. In analogy to the reduction step shown in Figure 4C, the reduced state of the Ir photocatalyst later returns the electron to complete the catalytic cycle by converting Ni(I) to Ni(0). In this case, the reactivity cannot be carried out with a stoichiometric oxidant because a low-steady state of Cl• is required, demonstrating that a multimetallic approach results in fundamentally new reactivity.

Sequential Activation and Capture of a Reactive Intermediate

Multimetallic catalysis can also enable reactivity inaccessible with monometallic systems through the separation of substrate activation and functionalization steps. Specifically, one catalyst can activate the substrate into a new, more reactive form, and the second catalyst can capture that species to make new chemical bonds. By separating reactivity in this way, each catalyst can be tailored for steps that might not be possible in a reaction catalyzed by a single metal.

A particularly useful version of the activation and subsequent capture approach is merging a catalyst that forms a radical intermediate with a catalyst that can capture and functionalize the radical (Figure 5A). Despite their reactivity, two advantages of using radical intermediates are that 1) they are compatible with many functional groups and reaction conditions, and 2) potential radical side reactions can be avoided because radical capture steps by metal catalysts can be very fast.[79] When combined with radical chemistry, polar transition metal-catalyzed reactions enable access to traditionally challenging bond-forming reactions. For example, high energy radical intermediates can allow for formation of sterically hindered products after trapping and bond formation. Notably, a variety of feedstock alkyl starting materials can be easily converted to radicals but do not typically participate in oxidative addition steps (e.g., carboxylic acids and amines).[80] Finally, using a catalytic amount of the radical-generating metal ensures only small quantities of the reactive radical intermediate is present in solution, which can enhance cross-selectivity between the two coupling partners and minimize off-cycle steps.

One of the most common approaches for generating radicals in multimetallic processes involves photoredox catalysis. In the presence of a substrate susceptible to reduction or oxidation, a radical can be generated by the excited photocatalyst that can be subsequently captured by a second metal. As an early example, Sanford and coworkers disclosed a C—H arylation of 2-arylpyridine derivatives catalyzed by $Pd(OAc)_2$ and $Ru(bpy)_3Cl_2$ under visible light irradiation (Scheme 8).[81] High-energy aryl radical generation proceeded via reduction of an aryldiazonium salt by a Ru photoredox catalyst. Aryl radical capture by an arylpalladium(II) intermediate, the resting-state of the catalyst derived from C—H activation of a phenylpyridine substrate, and subsequent C—C bond formation provided the desired products. Compared to a thermal reaction, this C—H arylation proceeded at significantly lower temperature (25 °C vs >100 °C), once again highlighting the often-mild nature of radical processes integrated with cross-coupling.

Given the proclivity of first row transition metals to both generate and accept reactive radical species, reduction or oxidation of an organic substrate by photoexcited Ir or Ru dyes to an alkyl radical, followed by radical capture at Cu or Ni, has proven to be a general step in $C(sp^3)—C(sp^2)$ and $C(sp^3)—C(sp^3)$ bond-forming reactions.[63,64,80] While we note that this strategy is not always multimetallic – organic dyes or single catalysts can suffice in some cases – the most general approach within this paradigm appears to be multimetallic.

More broadly, radical capture at organonickel(II) is central to a growing array of $C(sp^3)—C(sp^2)$ and $C(sp^3)—C(sp^3)$ bond-forming methods.[65] In early work, the Ni catalyst both generates and captures the radical, but this can lead to poor selectivity with some substrate pairs. To overcome this challenge, two distinct catalysts can be used: one that only participates in radical generation (wide variety of catalysts), and one that is responsible for activation of an electrophile, radical capture, and reductive elimination (Ni).[82-84] These lessons have increasingly been translated to Cu catalysis.[85-87]

Variation in the radical generation method plays a key role in the scope of a reaction and the associated functional group compatibility. As discussed previously, metallaphotoredox catalysis forms radicals from substrates that are easily reduced or oxidized via single electron transfer that are then efficiently captured by an organonickel(II) intermediate to form products. In some cases, outer-sphere electron-transfer requires unreasonable potentials, limiting functional group compatibility. For example, alkyl halides are more difficult to reduce than aryl halides by electron-transfer but react faster than aryl halides by halogen atom transfer (XAT). This challenge can be overcome by introduction of another catalyst that can mediate radical generation via other mechanisms, such as hydrogen atom transfer (HAT), ligand-to-metal charge transfer (LMCT), or XAT.

The addition of catalytic Ti complexes is one strategy to facilitate the generation of aliphatic radicals. Reactivity of Ti(III) complexes has been established to undergo ring-opening of epoxides via coordination of the epoxide to Ti followed by single electron transfer to generate β-alkoxy radicals (Figure 5B).[88] Here, the regioselectivity for radical generation can be described by formation of the more-substituted, and thereby stable, radical. This system was leveraged by our groups[89,90] and others to supply radicals for Ni-catalyzed C—C bond formation, enabling the general use of epoxides, non-traditional reaction electrophiles, in metal-catalyzed cross-electrophile coupling reactions. This general paradigm was also employed by Lin and coworkers in rearrangement of epoxides to allylic alcohols via Ti/Co catalysis (Scheme 9).[50] Ti(III) is proposed to promote ring opening of the epoxide, and the resulting Ti(IV)-bound β-alkoxyl radical can undergo HAT or proton-coupled electron-transfer (PCET) with a Co(II) species, thereby producing an alkene. After deprotonation of the cobalt hydride, a redox reaction between cobalt and titanium closes the catalytic cycle.

Another class of radical-generating co-catalysts are nucleophilic cobalt complexes. These Co catalysts can participate in polar S_N2 reactions with subsequent homolysis of the weak Co(III)—alkyl bond to form radicals. Building upon Cr/Co studies by Takai, Utimoto, and Kishi,[91,92] we found that cobalt phthalocyanine (Co(Pc))[93,94] could serve as a co-catalyst for benzylic radical generation from benzyl mesylates[51]; in contrast to radical generation by electron transfer, Co(Pc) generates radical species after 2-electron nucleophilic substitution, providing a method for C—O bond activation not accessible by electron transfer pathways (Figure 5C). In the cross-coupling of a benzyl mesylate (generated *in situ* from a benzyl alcohol) with bromobenzene, we found that use of either (dtbbpy)$NiBr_2$ or Co(Pc) without the other catalyst resulted in trace or no yield. Employment of both catalysts resulted in cross-coupling to the corresponding diarylmethane in 73% yield, with no homocoupling of the benzyl radicals observed. This system has been extended to primary alkyl bromides by utilizing a different reductant (tetrakis(dimethylamino)ethyelene, TDAE).[95] It has also been applied to systems utilizing more inert electrophiles such as alkyl tosylates[52,96,97] and epoxides[98] by replacing Co(Pc) with a more nucleophilic Co catalyst,-Vitamin B_{12}.

Metal hydrides with weak M—H bond strengths can react with alkenes by HAT to form alkylmetal or alkyl radical intermediates. This approach is complementary to the more common polar methods of alkene activation, which are often limited by sterics and regioselectivity challenges.[99] Shenvi recently demonstrated two systems based upon Ni/Co[100,101] and Ni/Fe[102] multimetallic catalysis that effect the hydroarylation of alkenes by two distinct mechanisms. In the Ni/Co system, the Co(salen) catalyst reacted with a hydride source (PhSi(*i*-PrO)SiH_2) and terminal alkenes to form stable alkylcobalt intermediates that could then be transferred to the Ni cross-coupling catalyst. In contrast, the Ni/Fe system relied on free radical generation upon interaction of an Fe hydride with the alkene, followed by radical capture at Ni (Scheme 10). This HAT/radical capture system required matching the rate of radical generation by Fe with the product-forming nickel cycle. For example, $Co(acac)_2$ was too active a HAT catalyst and Ni/Co reactions led to olefin hydrogenation and hydration without productive hydroarylation. A less active HAT catalyst (Fe),[103] provided high yields of hydroarylation product in this system. Most recently, this system has been extended to the hydroalkylation of alkenes with unactivated alkyl halides using Mn/Ni catalysis.[104]

Domino Multimetallic Reactions

Understanding the mechanisms of how metal catalysts activate organic substrates can guide the design of new multimetallic processes that allow for the formation of a number of bonds in a reaction. In this class of multimetallic reaction, one of the catalysts activates a substrate and causes a rearrangement into a second, more reactive intermediate that is then able to react with the second catalyst to form product (Figure 6A). These reactions share elements of domino[105,106] and multimetallic catalysis because one or both metals serve two roles – activating a substrate as well as modifying that fragment before reaction with the second metal catalyst.[10] This type of reactivity has also been termed “catalyzed catalysis.”[107] For example, Blum reported the synthesis of substituted butenolides and isocoumarins with an Au/Pd dual catalytic strategy (Figure 6B).[107] The π-acidic Au catalyst facilitates cyclization of an ester oxygen onto an alkyne or an allene to form an *O*-allyl oxonium intermediate that is primed to react with Pd, forming an electrophilic π-allyl Pd species and a nucleophilic vinylgold species. After transmetalation of the vinyl species from Au to Pd, reductive elimination forms the product. While Au-catalyzed cyclizations of this type are well known, the reactions are usually terminated by protodeauration.[108,109] By connecting this reaction to Pd π-allyl chemistry, C—C bond formation is enabled instead.

Despite the success of the Blum study, Au and Pd multimetallic reactions can suffer from several side reactions that are emblematic of challenges in multimetallic catalysis: redox compatibility and issues related to catalyst turnover. For example, Gagné noted that $(R_3P)AuOAc$ can oxidize Pd(0) to Pd(II) with formation of a Au(0) mirror on the glass surface.[13] This could be suppressed with the use of NHC ligands on Au, demonstrating the central importance of ligand choice. Secondly, Hashmi noted stoichiometric coupling of aryl iodides with organogold reagents but could not achieve catalytic turnover due to the high stability of (L)Au—I (albeit this species could be recovered and reactivated with AgOTs).[110] Interestingly, Hashmi also noted that transmetalation from Au to Pd was essentially irreversible (*vide infra*). These limitations could be overcome, for example, in Au/Pd Sonogashira couplings[111] and in Au/Pd cycloisomerization/cross-coupling cascades to prepare arylated butenolides.[112] In the Au/Pd-catalyzed synthesis of butenolides reported by Nevado, an extensive screen of conditions led to a solution for turnover of both metals (Scheme 11): in general, multimetallic strategies involving gold should be designed to reactivate, or avoid the formation of, catalytically inactive (L)AuX species. Here, employment of a more activated phosphine-ligated AuOAc catalyst (rather than the chloride analog) with electron deficient ancillary ligand $P(p\text{-}CF_3Ph)_3$, acetate base co-catalysis (10 mol% CsOAc), elevated temperatures (80 °C), and greater concentration (1.2 M) all proved essential for driving the impressive cross-coupling cascade.

All of the above domino multimetallic examples form product via a monometallic reductive elimination. Another possibility within this class of reactions is a bimetallic bond forming process. For example, the Trost group combined the reactivity of π-allyl Pd(II) intermediates with *in-situ*-formed vanadium allenoates (Scheme 12).[113] The reaction proceeds by two distinct substrate activation modes followed by attack of the nucleophilic enolate on the electrophilic π-allyl Pd(II) species. First, transesterification between $V(O)(OSiPh_3)_3$ and a propargylic alcohol generates a vanadium ester, which then undergoes a 1,3-transposition to form the nucleophilic V-allenoate.[114] Attack of this species on a bisphosphine-ligated π-allyl palladium(II) intermediate generates an α,β-unsaturated ketone product. Both transient intermediates are susceptible to other pathways: the nucleophilic vanadium intermediate could undergo protonation (Meyer-Schuster rearrangement product) while the electrophilic π-allyl Pd(II) species could undergo nucleophilic attack by alcohol present in reaction mixture. Indeed, a reaction employing only the V catalyst provided the Meyer-Schuster rearrangement byproduct exclusively, and a reaction employing only the Pd catalyst resulted in only the *O*-allylated alcohol byproduct. However, when both catalysts were employed, the desired allylated enone was prepared in 98% yield. The reaction selectivity could be controlled by changing the [V]:[Pd] ratio (optimized at 3:1 V:Pd). Higher loadings of either catalyst resulted in larger amounts of the corresponding, undesired side product.

Multimetallic Catalysis Enabled by a Transmetalation Step

In many multimetallic systems, substrate exchange between the two catalysts by a transmetalation step is pivotal and is usually turnover-frequency limiting (Figure 7A). While transmetalation of stoichiometric, pre-formed organometallic reagents is a key step in cross-coupling reactions (e.g., Zn to Pd in Negishi coupling),[115] selective transmetalation between two catalytic intermediates, each present in low concentrations and each bearing ancillary ligands, is less well understood and can be a barrier to reaction development. Limited studies on transmetalation between two transition metals have been reported, which can be used to inform multimetallic reaction design.[116-120] This area was reviewed by Casares and Espinet in the context of multimetallic reactions of group 10 metals.[3] Pioneering studies by Osakada and Yamamoto,[117] Puddephatt,[121,122] Cross,[123] and others on transmetalation between transition metals, primarily groups 10-12 (Ni, Pd, Pt, Cu, Hg), noted that the metal electronic structure, coordination sphere, and steric hinderance all contributed to an efficient process, suggesting a dinuclear bimetallic intermediate with bridging carbon and X-type ligands was key. More recently, Lewis has studied transmetalation from a variety of additional transition metals (Ir, Rh, Mo, W) to Pt, showing that a variety of groups could be transferred (-CH_3, -CH_2Ar, -Ph) and that steric effects impacted reaction rates; less hindered, lower-coordinate complexes reacted faster.[118,119,124] Both sets of studies noted that the nature of the organic fragment was also paramount to rate acceleration. While these studies provide general models for transmetalation, understanding is not yet at the level that successful transmetalation between two transition metals can be predicted with certainty. In addition to this challenge, a multimetallic reaction must also avoid off-cycle transmetalation that can lead to dimeric products. It is our view that an improved understanding of this step and how to engender selectivity is a major factor limiting multimetallic catalysis development. *In addition to new systems, fundamental studies on transmetalation between transition metals are needed.*

Combinations of Cu/Ag/Au with other transition metals are useful in multimetallic catalysis (*vide supra*) to facilitate transmetalation while preventing off cycle events. Notably, RM^{I} intermediates do not form dimeric products in the absence of an oxidant (to generate R_2M^{III}).[3,14] Indeed, Cu/Pd systems were among the first studied as part of the Sonogashira reaction as copper acetylides transmetalate with arylpalladium(II) intermediates readily,[125,126] but do not form di-yne products without an oxidant. This system is exceptionally robust and has been used extensively in the synthesis of natural products and complex materials.[14]

Reliable transmetalation has allowed for the development of many different multimetallic reactions that would be impossible with a single metal. Gooßen utilized the ability of Cu(I)[127,128] and Ag(I)[129] salts to generate aryl—M(I) intermediates by decarboxylation of Ar—CO_2M(I) in cooperation with Pd catalysis to generate biaryls from aryl carboxylic acids and aryl halides (Figure 7B). The system is now a standard approach to access biaryls and ketones. As previously noted, Buchwald has demonstrated the ability to unite Cu-catalyzed hydrometalation of olefins with Pd cross-coupling for the hydroarylation of alkenes (Figure 3B) via selective Cu to Pd transmetalation.[48,130-132] Collectively, these and other works with Cu/Pd catalysis (e.g., carboboration reactions)[45,46] demonstrate how one reliable multimetallic system can give rise to a diverse array of new chemistry.

The key challenge when developing systems without Cu, Ag, or Au is avoiding unselective transmetalation and statistical mixtures of products. Stoichiometric studies on d^{10} metal transmetalation suggest a crowded transition state with bridging carbon and halide ligands that requires partial ionization to proceed.[117,133] Indeed, more strongly coordinating ligands, like fluoride, have been reported to suppress ionization and diminish dimeric side-product formation in monometallic cross-coupling reactions of Grignard reagents with aryl halides.[134]

Selective transmetalation between two different palladium catalysts plays a role in the selective C—H arylation of pyridine *N*-oxides by aryl halides, first reported by Fagnou (Figure 7C).[135] Mechanistic studies by Hartwig revealed that the C—H activation and the subsequent arylation is facilitated by two different catalysts: a cyclometalated Pd species derived from $P(t\text{-}Bu_2CMe_2CH_2)Pd(OAc)$ (the complex after C—H activation of one of the methyl groups on $P(t\text{-}Bu)_3$) and the non-cyclometalated $P(t\text{-}Bu)_3Pd(X)$.[136] Indeed, the observation of an induction period with $P(t\text{-}Bu)_3Pd(Ar)(OAc)$, when <1% of the C—H activation and cross-coupling between the aryl ligand and a pyridine *N*-oxide proceeded, suggested this Pd species was not responsible for the C—H cleavage event. Instead, it was found that this complex decomposes to a cyclometalated dimer $[Pd(\mu\text{-}OAc)(\kappa^2\text{-}t\text{-}Bu_2PCMe_2CH_2)]_2$, which, when subjected to the reaction, matched yields achieved in the catalytic cross-coupling without an induction period. This example underscores the importance of understanding single steps, including transmetalation, even between two distinct metal catalysts derived from the same transition metal.

Ancillary ligands can be used to improve selectivity in transmetalation. For example, transmetalation of a vinyl group from Ni(II) to Cr(III) is a key step in the NHK reaction (Scheme 2).[137] A major side reaction is the formation of diene products by homocoupling of the vinyl iodide by unselective transmetalation between two vinylnickel(II) intermediates and reductive elimination. Kishi found that selectivity for transmetalation from Ni to Cr could be enhanced by the choice of ancillary ligands on Ni and Cr.[138] In another important report, heterobimetallic Ni/Cr catalysts (Scheme 13) were developed that allowed for selective, efficient reactions at low catalyst loadings (1-2 mol% vs the more typical 5-20 mol%).[33,139] By rendering the desired Ni-to-Cr transmetalation intramolecular, dimerization pathways could be suppressed. This bimetallic approach is attractive, but has thus-far been less explored.

In 2015, we disclosed a Ni- and Pd-catalyzed cross-Ullmann reaction (Scheme 14).[18] Aryl triflates can be selectively coupled with aryl bromides to form a variety of biaryls utilizing 5 mol% each of $(bpy)NiBr_2$ and $(dppp)PdCl_2$ as pre-catalysts. Consistent with what had already been established in the literature, (bpy)Ni(0) reacted much faster with bromobenzene than with 4-methoxyphenyltriflate[140] and (dppp)Pd(0) reacted faster with the aryl triflate than the aryl bromide.[141] In addition to a selective oxidative addition step, cross-selectivity was explained by the persistent metal effect (Figure 2B): (dppp)Pd(Ar)(X) (X = OTf or Br) is persistant because it is stable to self-reactivity and (bpy)Ni(Ar)(Br) is transient because it is generally reactive towards transmetalation. The proposed key step in this transformation was transmetalation between (bpy)Ni(Ar)(Br) and (dppp)Pd(Ar)(OTf). Direct transmetalation appeared to be operative as no arylzinc intermediates could be detected and the reaction proceeded using an organic reductant, TDAE, in place of Zn. This system has proven robust and has been extended to the coupling of aryl chlorides[142] and the synthesis of diverse biheteroaryls.[143]

While stoichiometric studies on transmetalation between two isolated complexes provide insight into this catalytic step (Cu/Pd, Ni/Ni), the variability of the mechanism depending on catalyst identity, reagents, solvents, additives, and stoichiometry can make optimization challenging. Trends have been observed by Negishi that carbon fragments transmetalate from less electronegative alkali and alkaline metals to more electronegative transition metals (forming a strong, polar M—X bond).[144,145] Additionally, in the Migita-Kosugi-Stille coupling, the order of R group transmetalation has been reported to follow the order: alkyne > vinyl > aryl > alkyl. However, it is also clear that there are outliers to each case and it has been noted that the equilibrium can also depend upon the ancillary ligands. This ambiguity requires a careful, systematic examination of different ligand-metal combinations (phosphine, pyridine, carbene, pincer) with R and X group fragments such that analysis of trends and predictions of group transfer become possible.

Transmetalation by Shuttle Catalysis

When direct transmetalation between two catalysts is slow, the process can be catalyzed by a third metal. This class of reaction is referred to as “shuttle catalysis”. In shuttle catalysis, a metal catalyst facilitates transfer of a substrate between two other metal catalysts (Figure 8A). In this way, one metal catalyst can be responsible for activating a substrate, a second metal catalyst can deliver that substrate from one metal to another, and a third metal catalyst can enable bond formation. We derived this terminology from the nomenclature of chain-shuttling polymerization (Figure 8C). Note that this definition of shuttle catalysis differs from the “shuttle catalysis” concept recently described by Morandi, in which a functional group is transferred between two substrates by a single catalyst.[146]

When transmetalation between two metals (Figure 8A, M_A and M_C) is rate-determining, or prohibitively slow, metals such as Cu, Ag, Au, or Zn (M_B) can provide a lower energy pathway by shuttling groups between the two catalysts via two facile transmetalation steps (M_A to M_B and then M_B to M_C). Copper iodide was shown to dramatically accelerate transmetalation between Pd and Pt,[147] and Zn has been shown to mediate aryl transfer between Pd complexes.[148] In a difluoromethylation of aryl halides, Shen demonstrated that silver can mediate transmetalation of difluoromethyl groups from Si to Pd.[149] In our own studies on the Ni/Pd-catalyzed cross-electrophile coupling of vinyl halides and vinyl triflates, the Zn reductant was found to be responsible for transferring a vinyl group between the two metals (Figure 8B).[19] Unlike the original Ni and Pd-catalyzed cross-Ullmann reaction,[18] Zn was essential for product formation when the more activated vinyl electrophiles were used. In this system Zn not only provided a facile path toward transmetalation but also enabled high selectivity by eliminating build-up of a reactive intermediate (Ni(vinyl)X) that would otherwise lead to unproductive dimerization.[19]

While the use of a third metal catalyst might appear unduly complicating and impractical, this concept is already utilized at scale in chain shuttling and coordinative chain-transfer polymerization reactions (e.g., Dow's ethylene–octene INFUSE™ olefin block copolymers).[150-152] In chain shuttling polymerization (Figure 8C), two catalysts with different selectivities for alkene incorporation exchange growing polymer chains via a chain shuttling agent (CSA, M_B in Figure 8C). In a key report, a zirconium bis(phenoxyimine) catalyst (M_A) and a hafnium pyridylamide catalyst (M_C) exhibited differences in monomer selectivity for ethylene-octene co-polymerization and achieved chain shuttling with $ZnEt_2$ as the CSA (M_B, Figure 8C).[21] The block size of the resulting block co-polymers could be changed by altering the amount of Zn CSA used. The new co-polymers exhibited strikingly different properties (e.g., improved clarity, different T_m/density profile) than the polymer produced without a CSA. In coordinative chain-transfer polymerization,[153] zinc mediates the exchange of growing polymer chains to and from the active catalyst to achieve a narrow molecular weight distribution and minimize the catalyst loading needed for lower MW polymers (as in Figure 8C, but $M_A = M_C$).[154-158] In both cases, direct polymer transfer between catalysts is slow compared to CSA transfer. In this way, shuttle catalysis can be considered a class of multimetallic reactions in which a third metal *catalyzes transmetalation between two metal catalysts*.

FUTURE OUTLOOK

Synthesis in the 21st century will continue to be propelled forward by questions of sustainability, efficiency, generality, and scale. Multimetallic catalysis is poised to be an essential strategy to address these challenges and it is primed for wider exploration and study. Indeed, a large and growing literature in the areas of synergistic, cooperative, and multimetallic catalysis demonstrates a shift in reaction development from single-catalyst systems to more complex ones.[1-8,159] In order for multimetallic catalysis to reach its full potential, the discovery of new systems and an improved understanding of how functional systems work is required. As we have shown, many of these lessons can be learned from established C—C bond forming reactions that have facilitated cross couplings, ring openings, and polymerizations. However, many potential metal combinations remain unexplored.

Therefore, in addition to continuing the development and study of established catalyst pairs, the field would greatly benefit from 1) further exploration of new catalyst pairs outside of groups 10 and coinage metals; 2) analytical tools to elucidate the mechanism of multimetallic systems, including those metal systems that may exhibit paramagnetism or undergo ligand exchange; and 3) a systematic documentation of how two or more metal catalysts interact (e.g., transmetalation, electron transfer, ancillary ligand exchange). In the latter case, one could envision the use of high-throughput experimentation (HTE), larger data sets, and computational tools being of particular value in finding new catalyst pairs.[160-163] A predictive understanding of catalysts and reaction conditions could enable a "mix-and-match" approach to multimetallic reaction development on a broad scale. It is our belief that these advances, in addition to the design principles in this perspective, would provide solutions to many of the remaining challenges in chemical synthesis.

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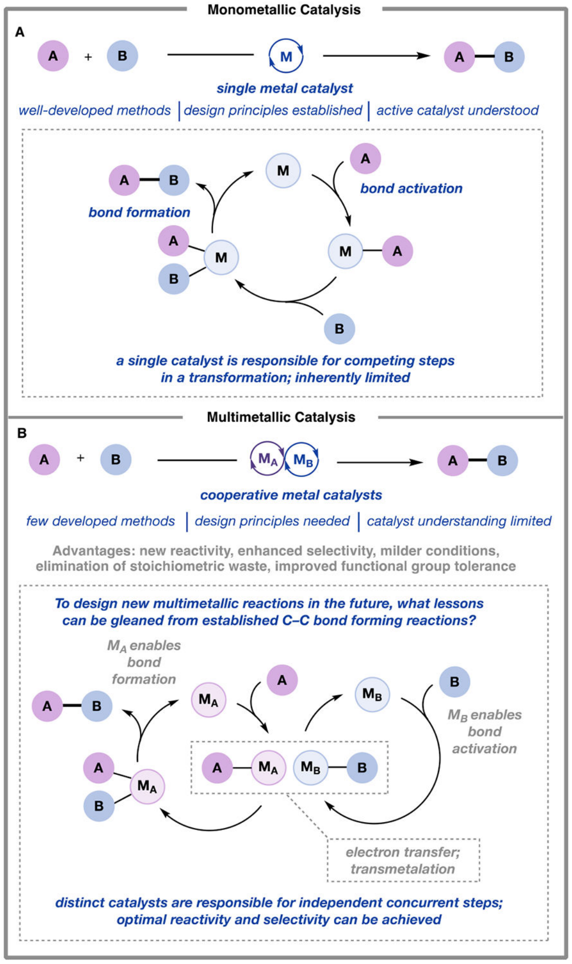


Figure 1.

Comparison of multimetallic catalysis (B) with monometallic catalysis (A).

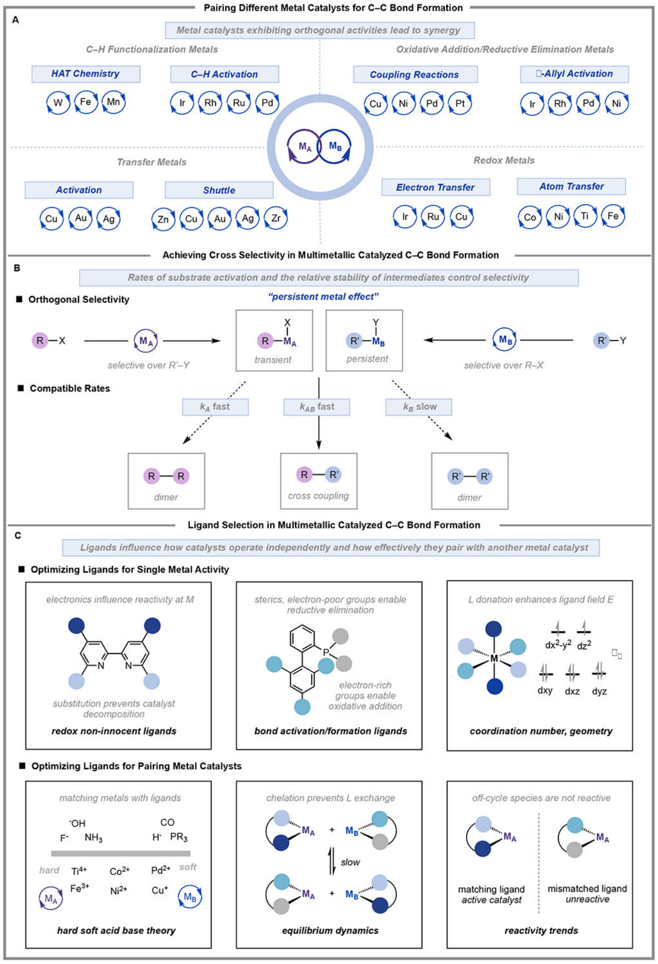


Figure 2. Design principles of multimetallic catalysis.

(A) Metals from different categories can be combined for new reactivity. (B) Selectivity in group transfer between metals can be controlled by the relative abundance and reactivity of the pair. (C) Factors to consider in ligand selection.

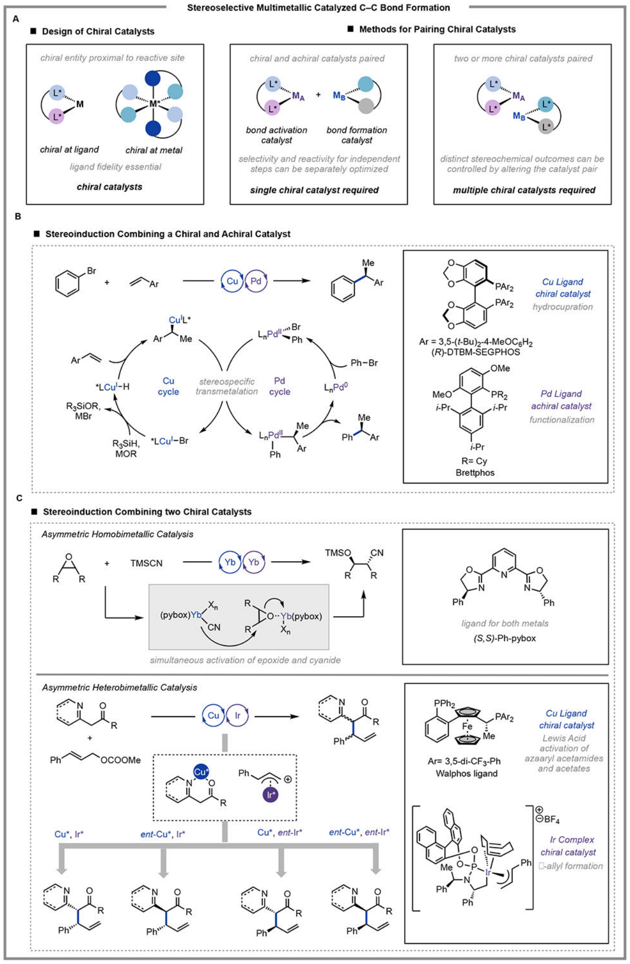


Figure 3.

Stereoselective multimetallic catalysis strategies (A) and selected examples for single-metal (B) and paired-metal (C) stereoinduction.

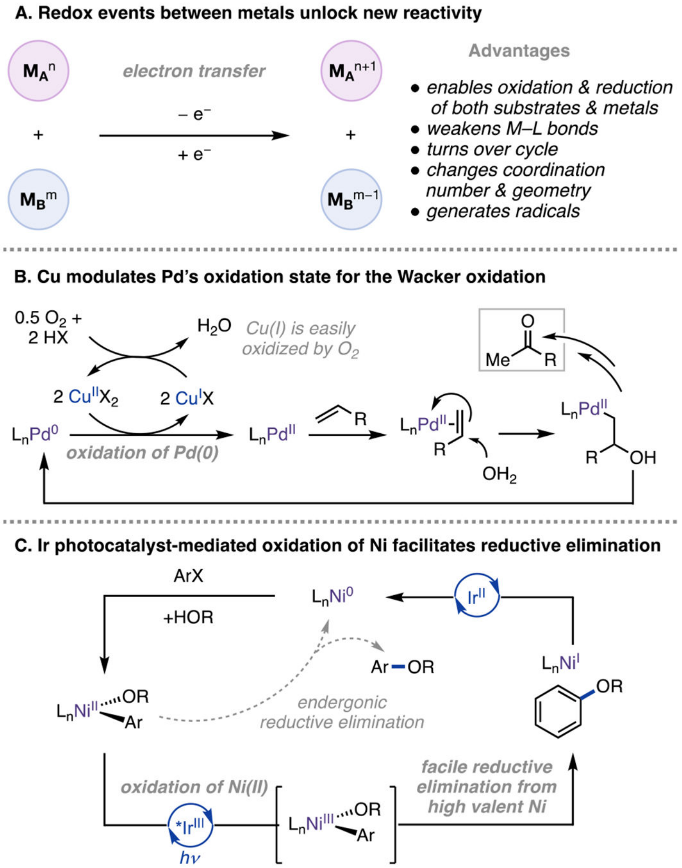


Figure 4.

Redox activation multimetallic catalysis concept (A) and examples showing a net oxidative process (B) and a net redox-neutral photoredox assisted process (C).

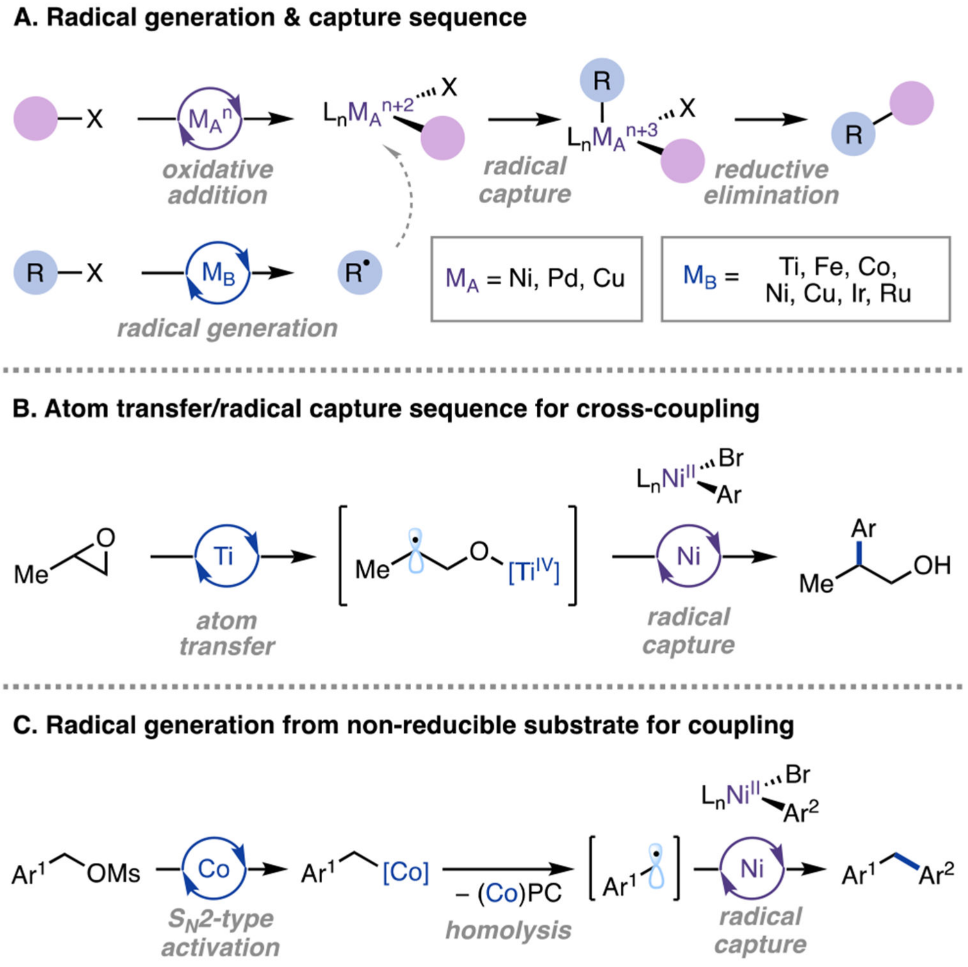


Figure 5.

(A) A general scheme for radical generation and capture in multimetallic-catalyzed processes and examples that generate radicals by (B) atom-transfer and (C) bond homolysis after an S_N2 reaction.

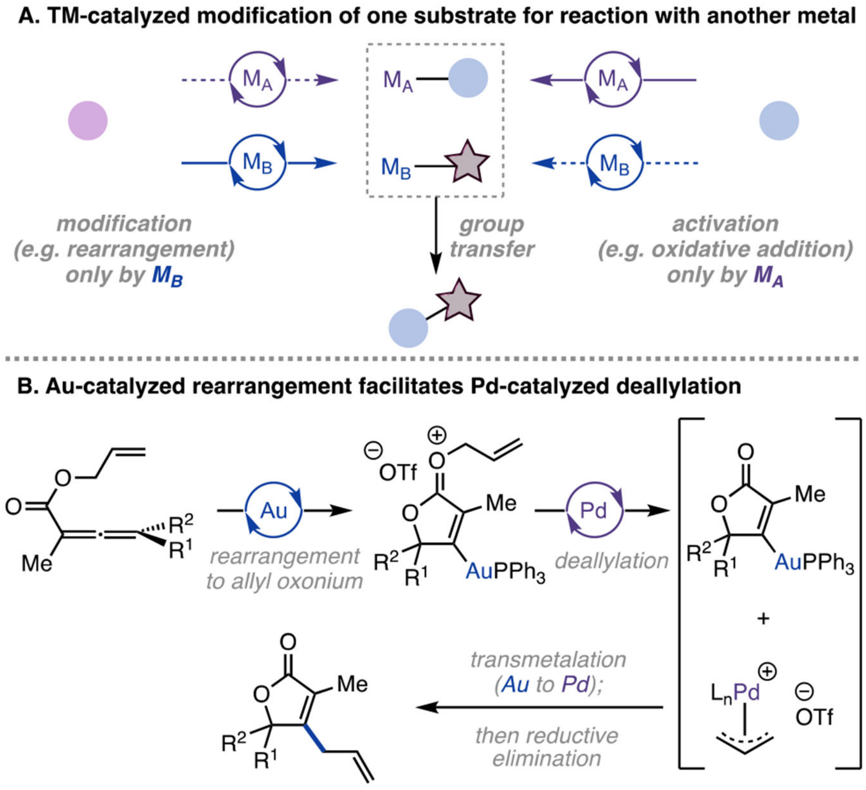


Figure 6.

Domino multimetallic reactions concept (A) and example (B).

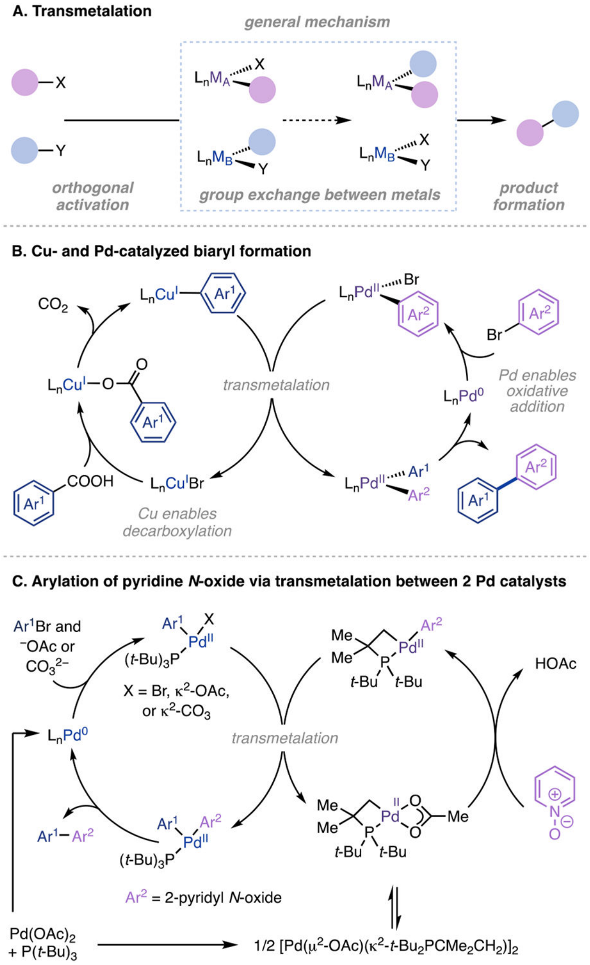


Figure 7.

Group transfer by direct transmetalation. (A) General mechanism of transmetalation between two metal catalysts. (B) Biaryl synthesis via transmetalation (Cu to Pd). (C) Transmetalation between two Pd catalysts in the direct arylation of pyridine *N*-oxide.

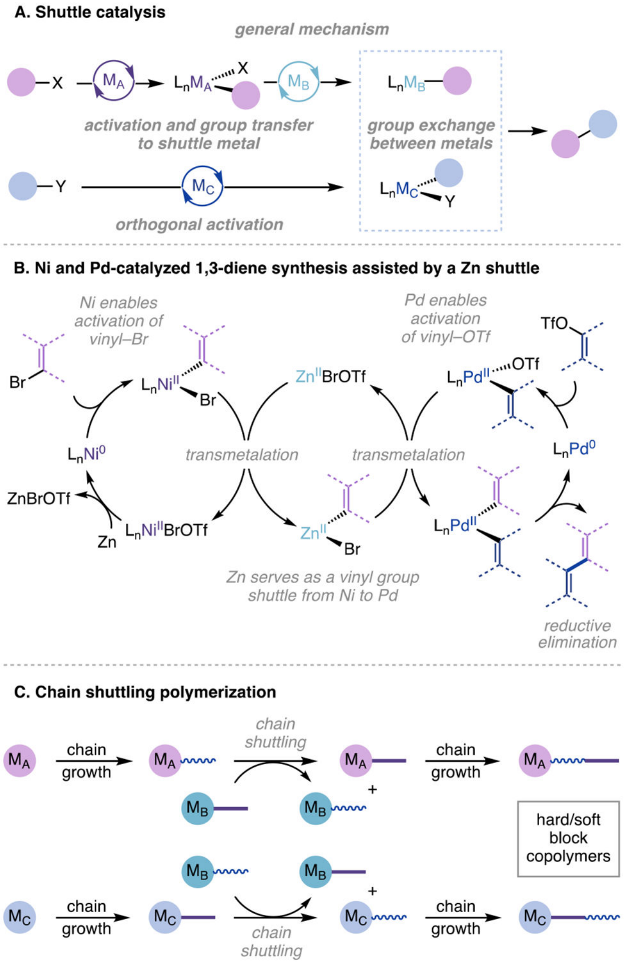
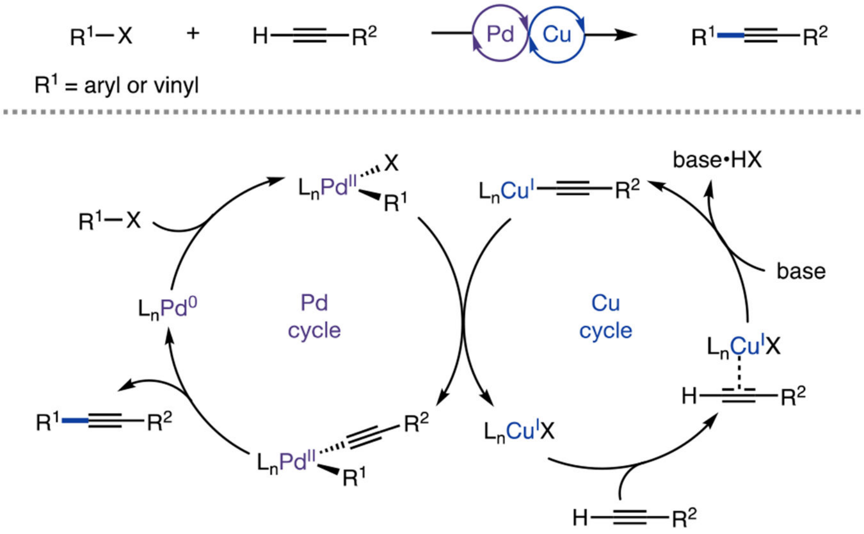
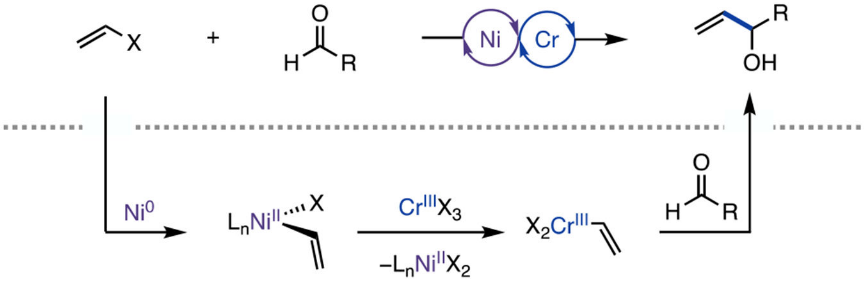


Figure 8.

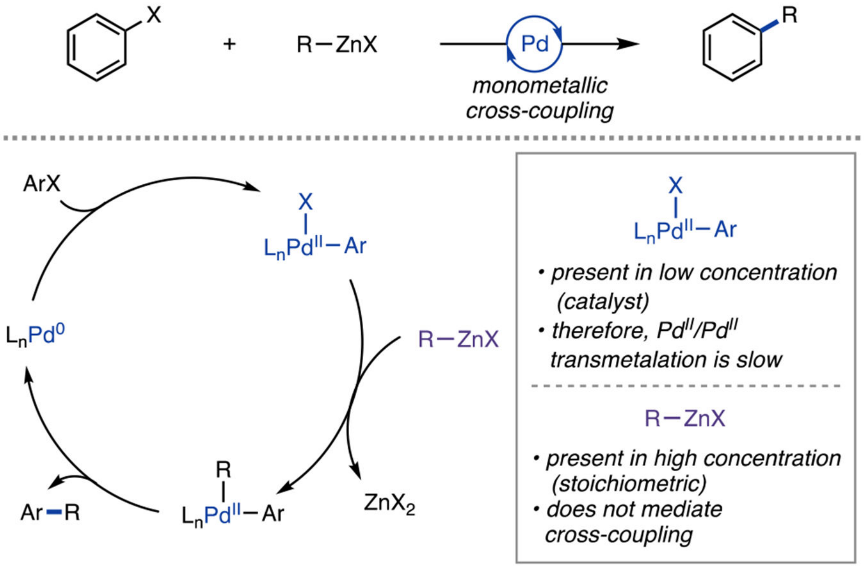
Shuttle catalysis. (A) General mechanism of shuttle catalysis. (B) Ni/Pd-catalyzed diene synthesis employing a Zn shuttle. (C) Chain shuttling polymerization involving two distinct metal catalysts (M_A and M_C, Zr and Hf) and a chain shuttling agent (CSA = M_B, Zn).



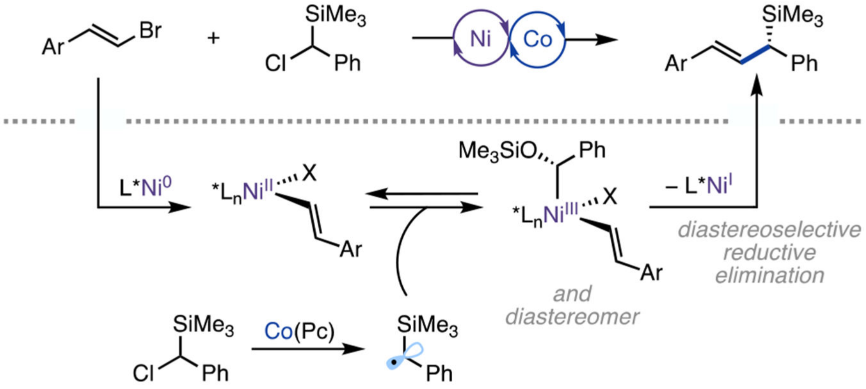
Scheme 1. Cu and Pd. The Sonogashira Reaction is a Prototypical Multimetallic Reaction.



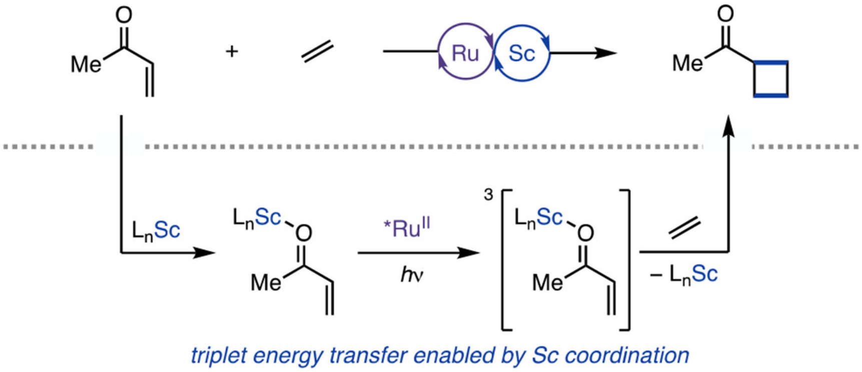
Scheme 2. Ni and Cr. Nozaki-Hiyama-Kishi Reaction Demonstrates Complementary Reactivity of Early and Late Metals.



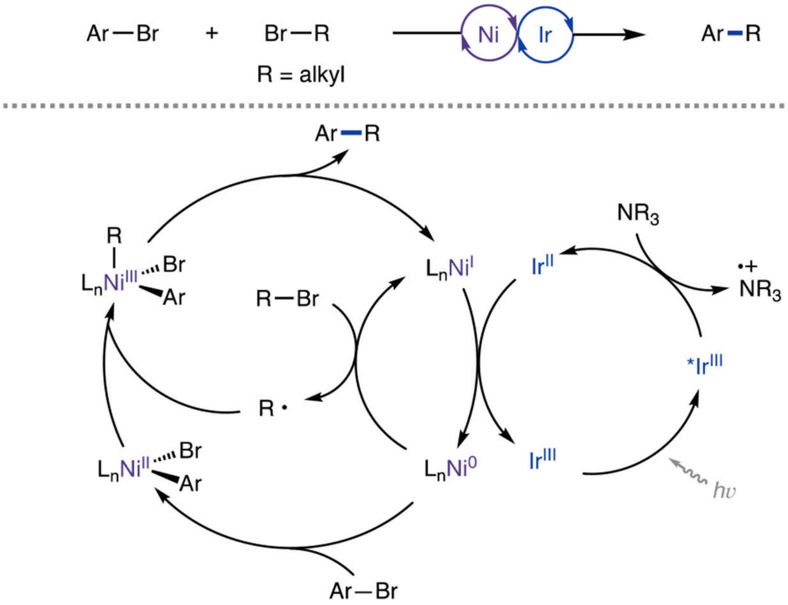
Scheme 3. Negishi Coupling Illustrates How Reactivity and Concentration Differences Can Influence Selectivity.



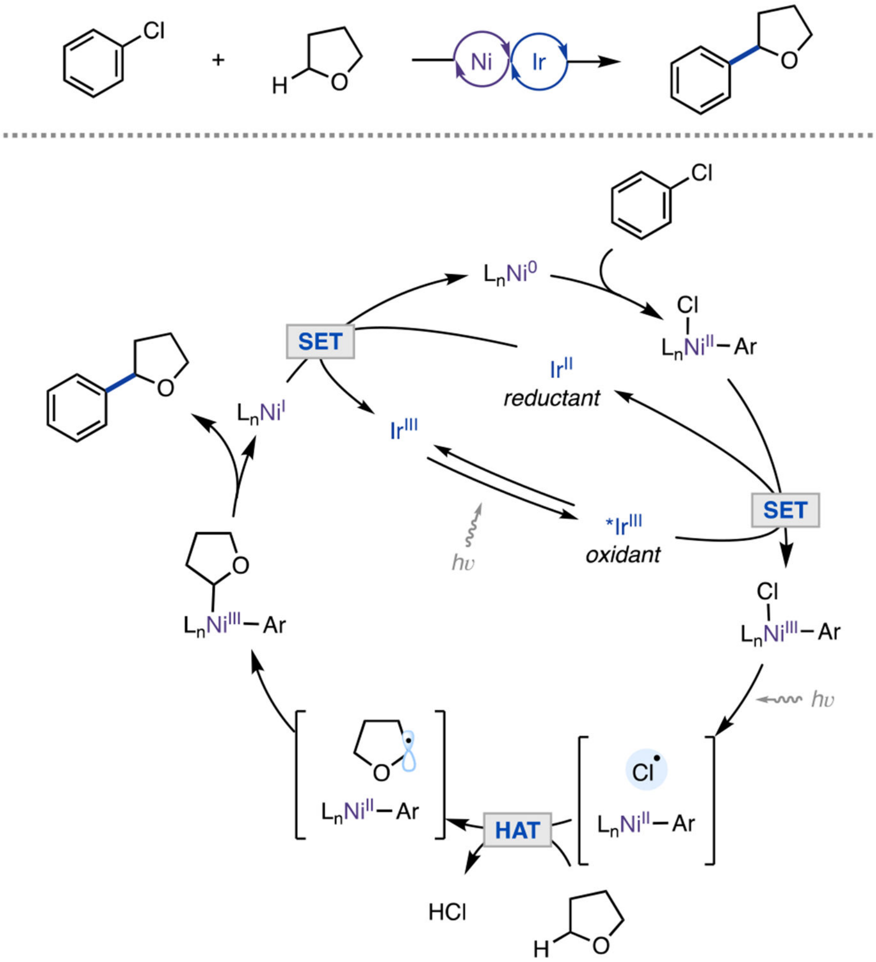
Scheme 4. Ni and Co. Enantioconvergent Cross-Electrophile Coupling By Stereoselective Reductive Elimination.



Scheme 5. Ru and Sc. Enantioselective Triplet Energy Transfer Enabled by Multimetallic Catalysis.

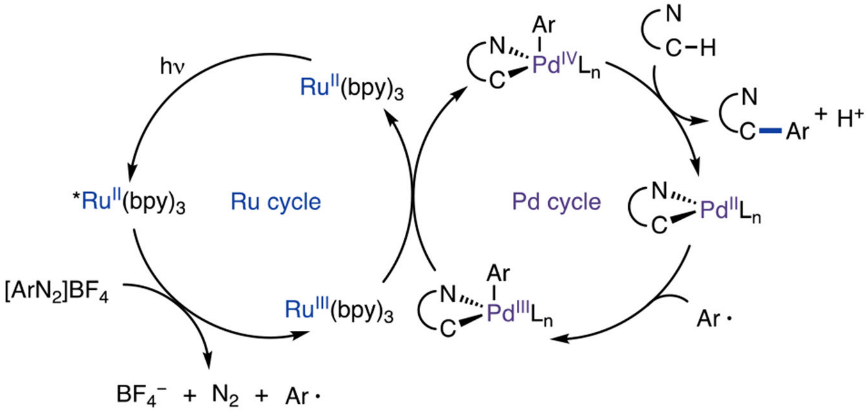


Scheme 6. Ni and Ir. Photoredox Assisted Cross-Electrophile Coupling Illustrating a Simple Redox Activation.

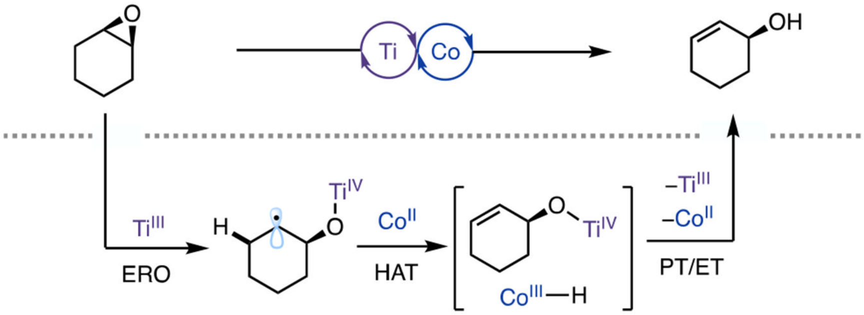


Scheme 7. Ni and Ir. Photoelimination Cross-Coupling Illustrates Redox Activation to Enable a New Elementary Step.[a]

[a] Adapted with permission from reference 68. Copyright 2016 ACS.

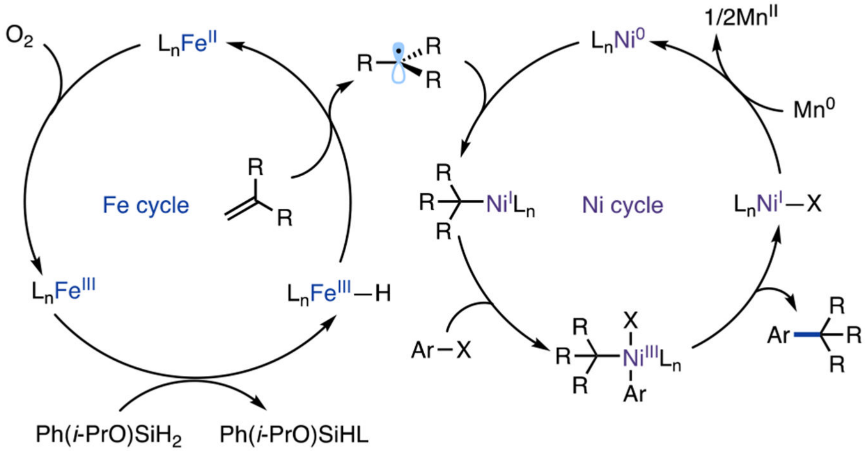


Scheme 8. Ru and Pd. Merger of Ar• with C—H Activation Enables C—H Arylation Under Mild Conditions.

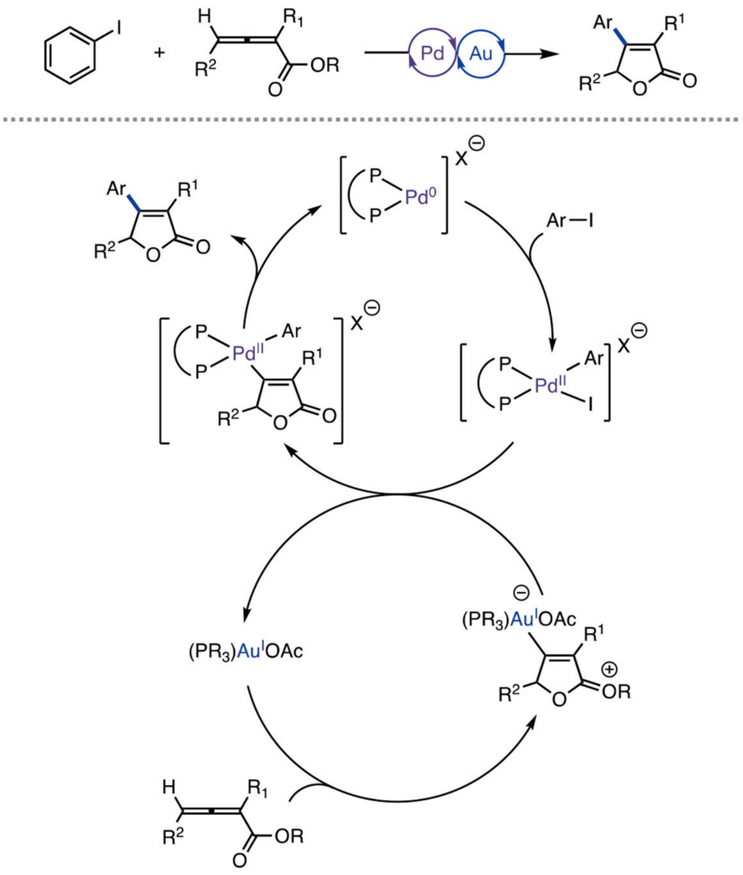


Scheme 9. Co and Ti. Reductive Epoxide Ring Opening Demonstrates Enantioselective Thermal Radical Formation.[a]

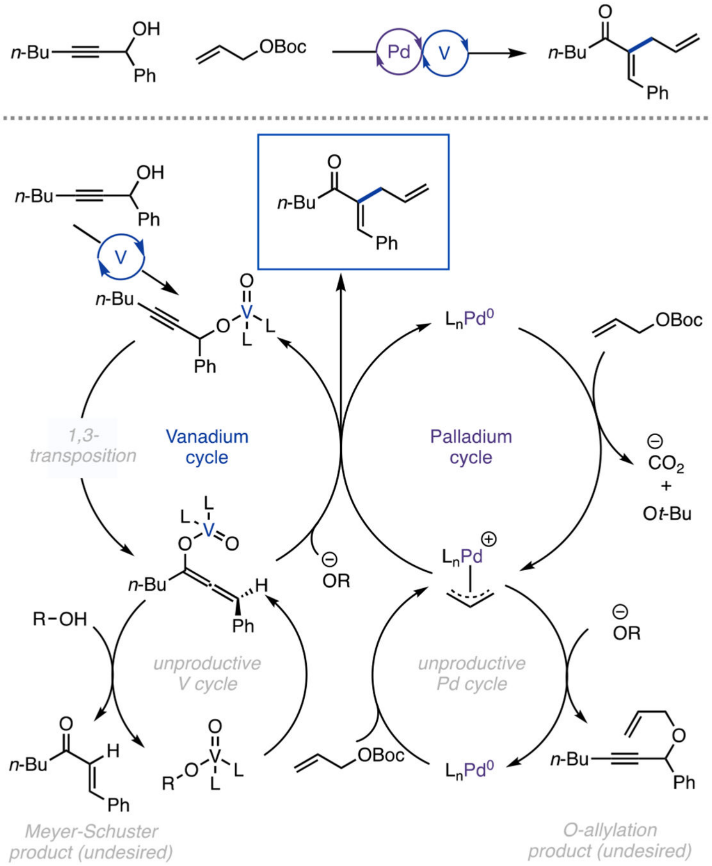
[a] ERO = epoxide ring opening; HAT = hydrogen atom transfer; PT/ET = proton transfer/electron transfer



Scheme 10. Fe and Ni. Merger of HAT and Cross-Coupling Enables the Hydroarylation of Alkenes.



Scheme 11. Pd and Au. Domino Multimetallic Activation, Rearragement, and Arylation of Allenoate Esters.



Scheme 12. Pd and V. Domino Multimetallic Activation, Rearrangement, and Allylation of Propargylic Alcohols.[a]

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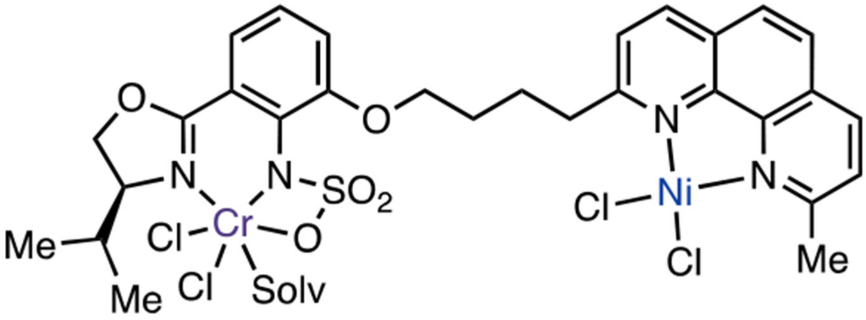
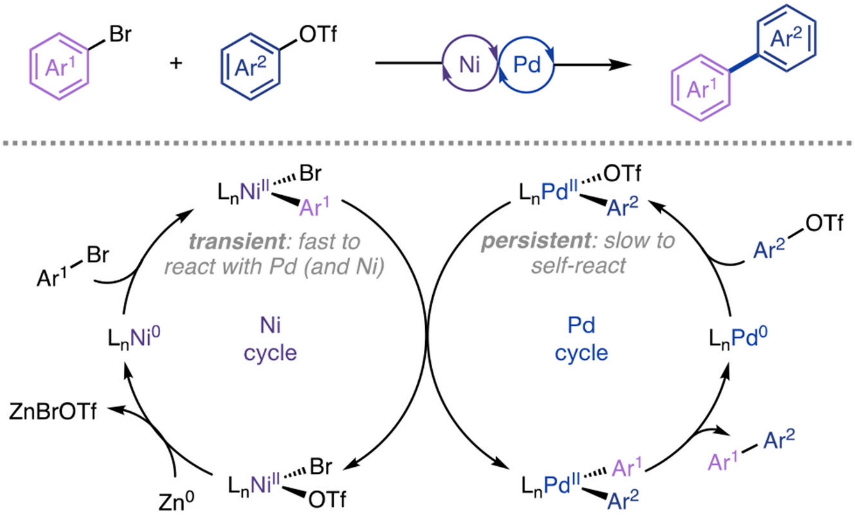


Scheme 13. Ni and Cr. A Heterobimetallic Catalyst for NHK Reaction that Accelerates Ni to Cr Transmetalation.



Scheme 14. Ni and Pd. Cross-Ullmann Reaction Illustrating Selective Transmetalation By the Persisent Metal Effect.