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Diverse Bimetallic Mechanisms Emerging from Transition Metal Lewis Acid/Base Pairs: Development of Co-catalysis with Metal Carbenes and Metal Carbonyl Anions

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The rational development of catalytic reactions involving cooperative behavior between two catalytic reactive sites represents a frontier area of research from which novel reactivity and selectivity patterns emerge. Within this context, this Feature highlights the development of a cooperative system involving transition metal Lewis acid/base pairs. Bimetallic systems consisting of copper carbene Lewis acids and metal carbonyl anion Lewis bases, (NHC)Cu-[M_{CO}], are easily synthesized from readily available organometallic building blocks (NHC = N-heterocyclic carbene; $[M_{CO}]^-$ = metal carbonyl anion, e.g. $[FeCp(CO)_2]^-$, $[Mn(CO)_5]^-$, etc.). Stoichiometric reactivity studies indicate that the dative Cu←M bonds in these systems are labile towards heterolysis under mild conditions, thus providing *in situ* access both to polar metal-metal bonds and to “frustrated” transition metal Lewis acid/base pairs as dictated by reaction conditions. Catalytic transformations ranging from C-C and C-B coupling reactions to hydrogenation and other reductions have been developed from both manifolds: bimetallic catalysis involving (a) binuclear intermediates engaging in cooperative bond activation and formation, and (b) orthogonal mononuclear intermediates that operate in either tandem or co-dependent manners. Preliminary indications point to the future emergence of novel reactivity and selectivity patterns as these new motifs undergo continued development, and additionally demonstrate that the relative matching of two reactive sites provides a method for controlling catalytic behavior. Collectively, these results highlight the fundamental importance of exploring unconventional catalytic paradigms.

Introduction

Homogeneous catalysis, particularly as applied to organic synthesis, has historically focused on catalytic systems with a single reactive site. A canonical example is the collection of palladium phosphine catalysts used for C-C and C-X coupling reactions (Chart 1a). While careful control of the phosphine ligands can be exploited to tune reactivity and selectivity patterns,[1] all the elementary steps required for catalysis are managed by a single palladium site that mediates all bond activation and formation processes as well as redox changes.

Moving beyond this prolific paradigm continues to be an active frontier area of catalysis research, with many exciting strategies being pursued concurrently (see selected examples in Chart 1).[2-4] For example, the use of redox non-innocent ligands allows for the metal and its supporting ligands to delocalize redox changes during catalysis while the single metal site mediates localized bond activation and formation processes (Chart 1b).[5-8] The use of chemically non-innocent ligands allows for bond activation and formation to be delocalized over two reactive sites (the metal and a ligand functional group) while redox changes are localized at one or the other (Chart 1c).[9-17] Similarly, frustrated Lewis pairs (FLPs) delocalize bond activation and formation over two reactive sites (Chart 1d).[18-21] These various strategies have been prolific in their ability to enable important chemistry with non-precious elements and/or to be venues for discoveries of emergent chemical reactivity that complements the behaviour of classic catalysts with a single reactive site.

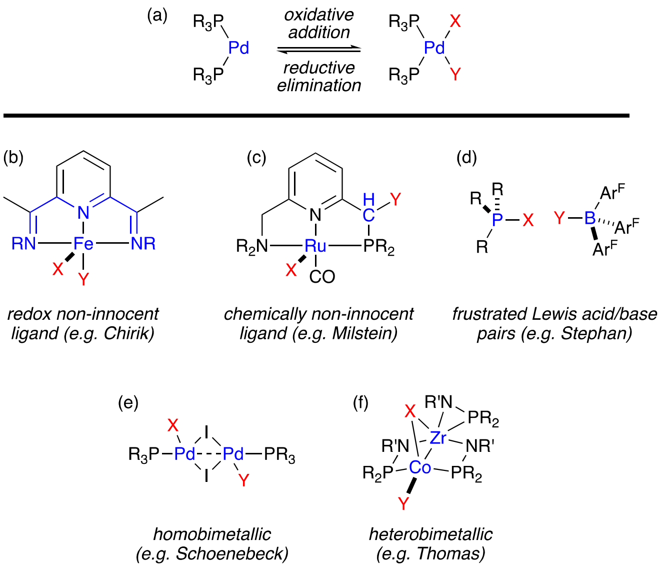

Chart 1. Examples of catalytic systems with (a) single-site and (b)-(f) multi-site reactivity.

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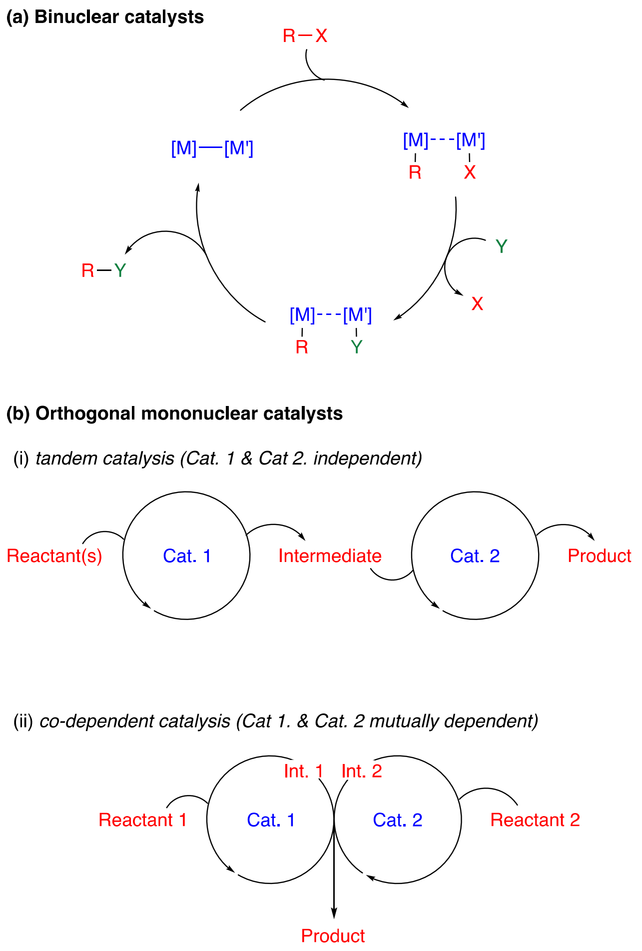
An additional approach to multi-site reactivity involves the use two or more metals.[22-24] For simplicity, this Feature will be limited to discussing only bimetallic systems. Complexes with metal-metal bonds of various bond orders have been long known to engage in binuclear bond activation reactions. Highly covalent systems, particularly homobimetallic complexes, hold tremendous promise in that, in principle, they can delocalize both bond activation/formation as well as redox cycling across two reactive metal sites (Chart 1e).[25-34] By contrast, less covalent heterobimetallic systems often resemble main group FLPs by delocalizing bond activation/formation over two metal sites, only one of which is redox active (Chart 1f).[35-39] The use of these binuclear bond activation/formation events in catalysis (Scheme 1a), both with homo- and heterobimetallic systems, is undergoing a resurgence from examination by many contemporary research groups.[40-58] Similarly, the development of catalytic transformations involving two monometallic co-catalysts with orthogonal reactivity (Scheme 1b) that operate in (i) independent (i.e. cascade or tandem reactions)[59-62] or (ii) co-dependent[63-70] manners without involving binuclear catalytic intermediates is an area of great topical interest.



Scheme 1. Catalytic schemes involving (a) binuclear bond activation/formation, and (b) two orthogonal mononuclear catalysts.

In this context, our group has studied a series of related heterobimetallic complexes from which many of these bimetallic catalytic mechanisms have emerged from a conserved catalyst design. Described below is the elucidation of this system that has given rise to catalytic transformations involving binuclear catalysis (C-H borylation, hydrogenation), orthogonal tandem catalysis (CO_2 deoxygenation), and catalysis involving co-dependent behaviour of two mononuclear co-catalysts (carbonylative C-C coupling).

Dynamic heterobimetallic catalysts

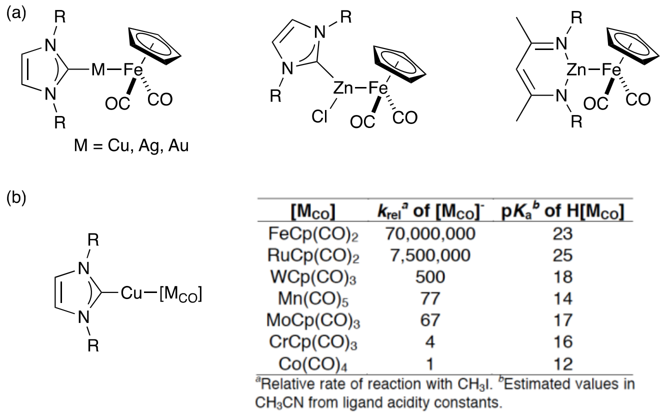
Synthesis and characterization

Inspired both by the chemistry of main group FLP systems and of bimetallic catalysts referenced above, our group sought to construct a collection of complexes exhibiting bifunctional reactivity between a transition metal Lewis acid and a transition metal Lewis base. The concept of "metal-only Lewis pairs" has been introduced recently,[71-73] but the area is in its infancy with regard to catalytic reaction discovery. Some of the earliest examples of this paradigm arguably are represented by "early-late" heterobimetallic complexes combining early metal electrophiles (typically of d^0 configuration) with well-known late metal carbonyl anions (typically of 18-electron valence counts).[36] These complexes have long been known to feature polar unsupported metal-metal dative bonds that give rise to cooperative bond activation reactions, although their applications to catalysis are limited.

$$\mathrm{Na[M_{CO}]} \quad + \quad \mathrm{L_nM{-}Cl} \xrightarrow[\text{- NaCl}]{\qquad} \mathrm{[M_{CO}]{\rightarrow}ML_n}$$

Scheme 2. Typical synthesis of heterobimetallic Lewis acid/base pairs featured here.

Our strategy has been to pursue a variation on this theme where the early metal is replaced with a late metal Lewis acid (typically of d^{10} configuration). Towards this end, we have compiled a wide range of heterobimetallic complexes, typically using an operationally simple salt metathesis synthesis involving trivial numbers of steps from commercially available precursors (Scheme 2). The vast majority of the complexes we have reported feature metal-metal bonds in the solid state and a 1:1 stoichiometry of the Lewis acidic and Lewis basic metal fragments. Only a small number of exceptions have been observed and include a small set of $\{(NHC)_2Cu\}^+\{[M_{CO}]\text{-}Cu\text{-}[M_{CO}]\}^-$ salts (NHC = N-heterocyclic carbene)[74] and a nickel pincer complex with isocarbonyl (Ni···O≡C-W) bridging rather than metal-metal bonding.[75,76] For the standard complexes discussed below, both computational analysis and spectroscopic data (XANES, Mössbauer)[77] are consistent with dative metal-metal interactions of a highly polar nature.



[M$_{CO}$]	k_{rel}[a] of [M$_{CO}$]$^-$	pK_a[b] of H[M$_{CO}$]
FeCp(CO)$_2$	70,000,000	23
RuCp(CO)$_2$	7,500,000	25
WCp(CO)$_3$	500	18
Mn(CO)$_5$	77	14
MoCp(CO)$_3$	67	17
CrCp(CO)$_3$	4	16
Co(CO)$_4$	1	12

[a]Relative rate of reaction with CH$_3$I. [b]Estimated values in CH$_3$CN from ligand acidity constants.

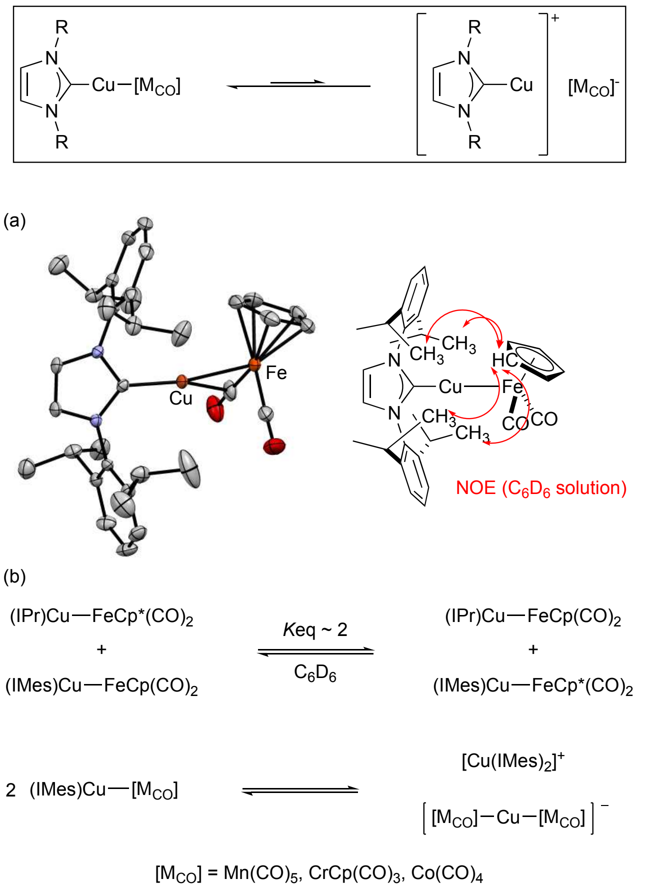
Chart 2. Heterobimetallic catalysts featured here: (a) various transition metal Lewis acids paired with the [FeCp(CO)$_2$]$^-$ Lewis base; (b) various metal carbonyl anions (with accompanying physical data[78-80]) paired with the [(NHC)Cu]$^+$ type Lewis acid.

Chart 2a shows such complexes reported by our group that consist of the canonical metal carbonyl anion, [FeCp(CO)$_2$]$^-$ or Fp$^-$,[81] combined with various late metal fragments that we used to commence our studies.[82-86] From these initial complexes, many of our reactivity studies have since been focused on derivatives of the (NHC)M-FeCp(CO)$_2$ motif, and especially for M = Cu. Chart 2b shows such (NHC)Cu-[M$_{CO}$] derivatives with various metal carbonyl anion fragments.[74] The electronic properties of these metal carbonyl anions are well established,[78-80] and so the behaviour of these heterobimetallic systems can easily be correlated with the relative electron richness/poorness of the [M$_{CO}$]$^-$ fragment in question (Chart 2b). While the complexes in Chart 2 were intended to feature dative metal-metal bonds *without* any bridging ligands, X-ray crystallographic studies indicate the presence of ≥1 "semi-bridging" CO ligands (Cu⋯C(O)M) in each derivative, presumably facilitated by the low-coordinate nature of the Cu(I) Lewis acid site. However, it should be noted that computational analysis has estimated these semi-bridging interactions to be of negligible energy values in the ground state (~6 kcal/mol).[87]

Solution dynamics and stoichiometric reactivity

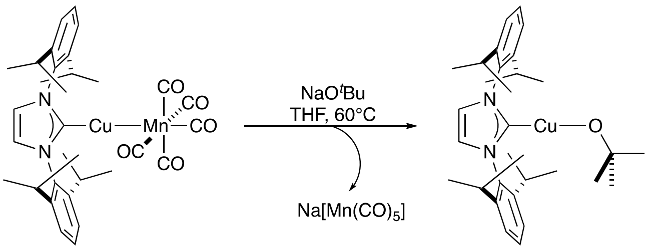
Several experimental observations indicate that the 1:1 metal-metal bonded forms of the complexes, as depicted in Chart 2, dominate in solution phase in the absence of external reagents (Scheme 3a). In addition to crystallographic characterization, high solubility of the complexes in non-polar solvents such as benzene is indicative of neutral rather than charged species. In all cases examined, only one set of NMR resonances was apparent by NMR spectroscopy. NOE data obtained for the (IPr)Cu-FeCp(CO)$_2$ derivative (IPr: R = 2,6-diisopropylphenyl in Chart 2b) indicated correlations between the NHC ligand on Cu and the Cp ligand on Fe, consistent with the [(IPr)Cu]$^+$ and [FeCp(CO)$_2$]$^-$ fragments being held close together in space by the dative metal-metal bond.[88]

However, several other experimental observations are consistent with the generation of small equilibrium concentrations of charge-separated [(NHC)Cu]$^+$[M$_{CO}$]$^-$ pairs in solution under mild conditions (Scheme 3b). First, crossover behaviour was observed between (IPr)Cu-FeCp*(CO)$_2$ and (IMes)Cu-FeCp(CO)$_2$ even at room temperature in benzene solution (IMes: R = 2,4,6-trimethylphenyl in Chart 2b). Because DFT calculations estimate a Cu-Fe homolytic bond free energy of ~58 kcal/mol for (NHC)Cu-FeCp(CO)$_2$ derivatives and because of the dative nature of the Cu←Fe bond, the observed crossover behaviour is more likely indicative of Cu-Fe heterolysis rather than homolysis.[88] Second, for cases where both the NHC ligand is the sterically smaller IMes and the [M$_{CO}$]$^-$ anion is weakly nucleophilic, (IMes)Cu-[M$_{CO}$] and {(IMes)$_2$Cu}$^+${[M$_{CO}$]-Cu-[M$_{CO}$]}$^-$ isomers could be independently characterized by X-ray crystallography depending on crystallization conditions.[74] Indirect evidence for solvent dependence of this isomerism also was noted for (NHC)Cu-FeCp(CO)$_2$ derivatives.[88] However, re-dissolution of {(IMes)$_2$Cu}$^+${[M$_{CO}$]-Cu-[M$_{CO}$]}$^-$ crystals gave identical spectroscopic signatures as re-dissolved (IMes)Cu-[M$_{CO}$] crystals by ^{1}H NMR, ^{13}C NMR, and solution-phase FT-IR, consistent with the equilibrium shown in Scheme 3 rapidly establishing itself in solution and greatly favouring the left hand side.[74] In other words, this systems exhibits characteristics of frustrated Lewis acid/base pairs.



Scheme 3. Proposed solution dynamics: (a) evidence for neutral 1:1 complexes in solution; (b) evidence for reversible metal-metal bond heterolysis. The Cu-Fe distance in (a) is 2.3462(5).

The above observations apply to the isolated heterobimetallic complexes in the solution phase. However, in the presence of some external reagents, quantitative separation of the two metals can be driven by trapping of one or both of the monometallic ions. For example, during our studies on Cu/Mn co-catalysed C-C coupling catalysis (vide infra), we found that the heterobimetallic species (IPr)Cu-Mn(CO)$_5$ was not stable when exposed to the stoichiometric alkoxide bases used under catalytic conditions, instead converting quantitatively to the monometallic pair (IPr)CuOR and $[Mn(CO)_5]^-$ (Scheme 3), presumably due to $[(IPr)Cu]^+$ being captured by alkoxide to drive the equilibrium away from the metal-metal bonded complex.[89] Generally, under catalytic conditions involving use of a reagent that binds as a X^- ligand to $[(NHC)Cu]^+$ more strongly than $[M_{CO}]^-$ does, it is reasonable to assume that the metal-metal bonded form of the heterobimetallic pair is not available in high concentrations and that reactivity instead involves two monometallic species, (NHC)CuX and $[M_{CO}]^-$. The orthogonal reactivity of these two species can be leveraged for various bimetallic mechanisms as outlined in Scheme 1b.



Scheme 4. Dissociation of a Cu/Mn heterobimetallic complex facilitated by an alkoxide base reagent.

In the absence of any external reagents that effectively trap either of the ionic species, it is reasonable to propose that reaction chemistry occurs through the metal-metal bonded manifold. Evidence for this assertion was studied in detail for the reaction of (NHC)Cu-[M_{CO}] complexes with alkyl halides. Having established that (NHC)Cu-FeCp(CO)$_2$ complexes react with methyl iodide to produce (NHC)CuI and CpFe(CO)$_2$CH$_3$,[82] the question we sought to address was whether reactivity was proceeding predominantly through the intact metal-metal bonded species or through small equilibrium concentrations of $[FeCp(CO)_2]^-$, which is a very reactive S$_N$2 nucleophile towards alkyl halides.[78,90] The reaction between (IPr)Cu-FeCp(CO)$_2$ and cyclopropylmethyl halide reagents was used as a probe to distinguish between these possibilities, as this probe has been used to study the chemistry of $[FeCp(CO)_2]^-$ previously.[91] While the behaviours of (IPr)Cu-FeCp(CO)$_2$ and $[FeCp(CO)_2]^-$ towards cyclopropylmethyl bromide were indistinguishable, distinct product distributions of the ring-opened and ring-closed alkyliron complexes were indeed observed with cyclopropylmethyl iodide under identical conditions.[84] These results are inconsistent with bimetallic activation of the alkyl halide occurring through the "unmasked" $[FeCp(CO)_2]^-$ from Cu-Fe heterolysis, which would be expected to produce an identical product mixture as that from $[FeCp(CO)_2]^-$, and instead indicate direct activation of alkyl halides by the intact Cu-Fe bond.

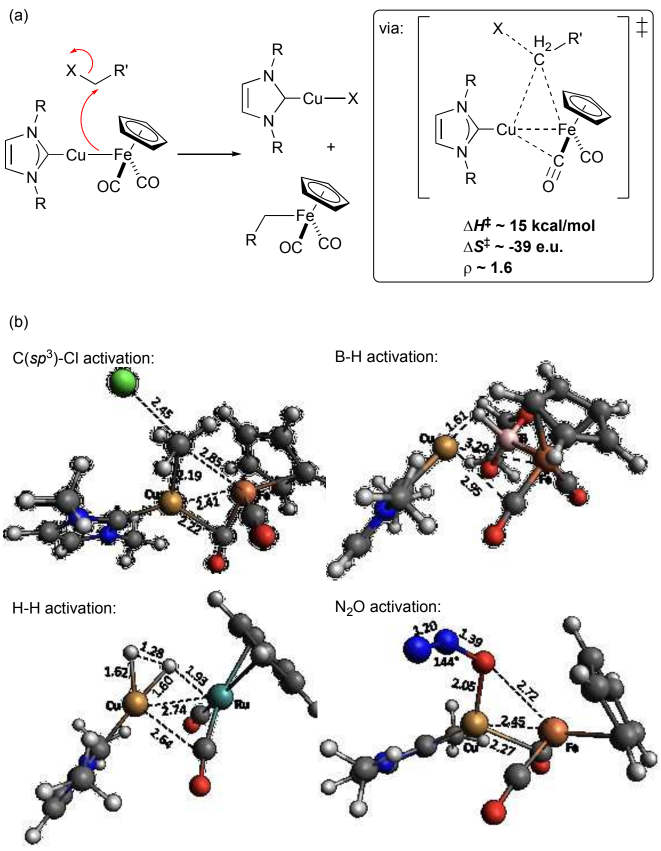


Figure 1. (a) Transition state schematic for bimetallic activation of alkyl halides, (b) transition state models for bimetallic C-Cl, B-H, H-H, and N-O activation calculated by DFT.

The transition state for bimetallic activation of alkyl halides was characterized both experimentally and computationally (Figure 1a).[84] The activation parameters for reactivity towards benzyl chloride include a large and negative activation entropy approaching -40 e.u., indicating a highly organized transition state. The Hammett reaction constant (+1.6) for reactivity towards *para*-substituted benzyl chlorides indicates a build-up of negative charge on the alkyl halide carbon centre in the transition state. A computational model for the transition state features the alkyl halide undergoing halide displacement with inversion of stereochemistry at carbon, as the carbon centre engages with the metal-metal bonding electrons. It is noteworthy that this model indicates templating of the bimetallic transition state by one of the two carbonyl ligands, which occupies a bridging position in the transition state to provide stability as the Cu-Fe bond elongates (Figure 1b). Empirical observations indicate that the activation energy for alkyl halide cleavage increases significantly when $[FeCp(CO)_2]^-$ is replaced with a less nucleophilic $[M_{CO}]^-$ such as $[RuCp(CO)_2]^-$ (see Chart 2) or when Cu is replaced with more electronegative Ag or Au.

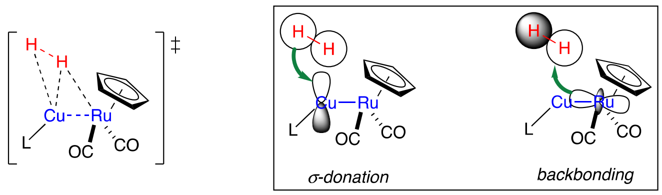
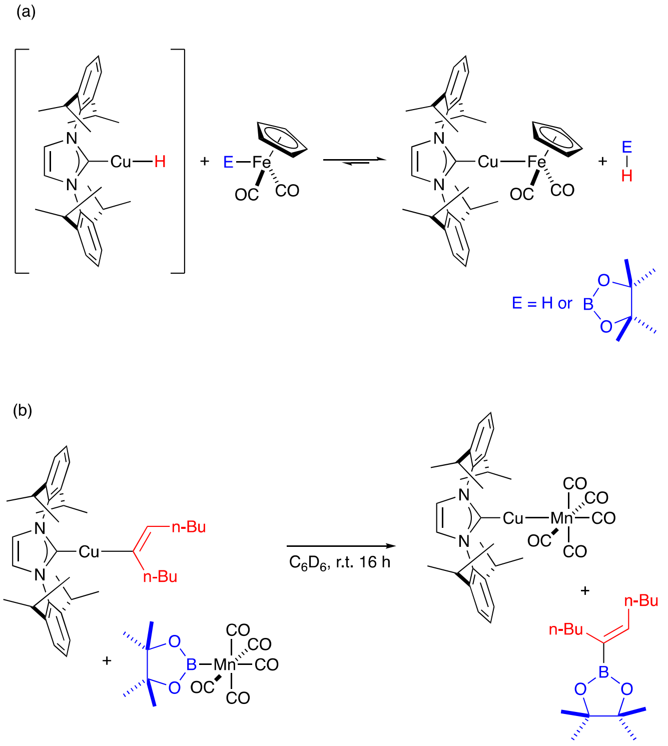


Figure 2. Key orbital interactions leading to heterobimetallic H-H activation.

Topologically similar transition states were calculated for catalytically relevant (vide infra) bimetallic activation of B-H,[88] H-H,[92] and N-O bonds (Figure 1b).[83,93] We also presume that a similar transition state is operative during insertion of CS_2 into the Cu-Fe bond of (NHC)Cu-FeCp(CO)$_2$ complexes.[83] For the bimetallic activation of H_2 by a Cu/Ru model system, reaction coordinate-dependent NBO calculations indicated that the dominant charge transfers during H-H cleavage are (a) from the filled σ_{HH} orbital into a Cu 4*p*-like orbital, and (b) from a Ru 4*d*-like metal-metal bonding orbital into the empty σ^*_{HH} orbital (Figure 2).[92] Presumably, these are the key orbital interactions that lead to heterobimetallic H-H activation. One can think of these as the heterobimetallic analogues of the canonical single-site σ-donation and π-backdonation, but here decoupled over two metal sites.



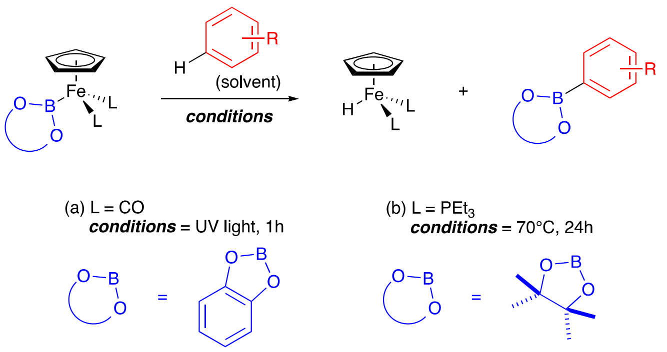
Scheme 5. Bimetallic formation of (a) E-H and (b) B-C bonds.

The B-H and H-H bond activation processes have been shown through stoichiometric reactivity experiments to be reversible, in fact favouring bimetallic B-H and H-H bond formation rather than cleavage (Scheme 5a).[86,88] In addition, an interesting B-C bond forming reaction was observed when an alkenylcopper species was reacted with an appropriate borylmanganese complex (Scheme 5b).[75] Thus this heterobimetallic system is capable of both bond activation and bond formation, providing the tools necessary to conduct bifunctional catalytic transformations.

Heterobimetallic catalytic transformations

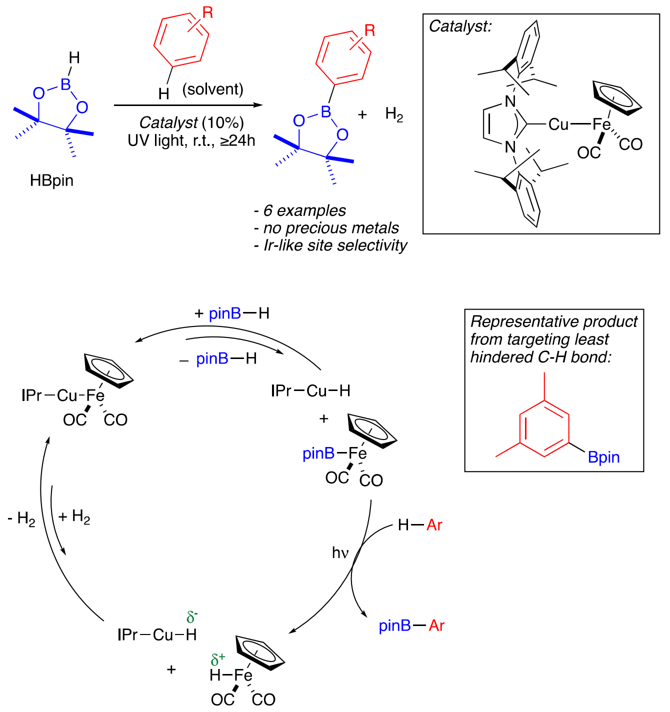
Binuclear catalysis

Borylation of C-H bonds. Our initial proof of concept study involved catalytic C-H borylation by binuclear catalysis. Borylation of C-H bonds typically utilizes Ir catalysis operating by a single-site Ir(III)/Ir(V) oxidative addition/reductive elimination mechanism.[94] The predecessors to these elegant catalytic C-H borylation technologies were stoichiometric C-H borylation reactions discovered by Hartwig's group in the mid-1990s.[95] Boryl complexes of $[M_{CO}]^-$ species, e.g. CpFe(CO)$_2$B(OR)$_2$ and Cp*W(CO)$_3$B(OR)$_2$, were shown to mediate stoichiometric borylation of unactivated arenes present in solvent quantities upon irradiation with UV light (Scheme 6a).[96-99] Catalysis was not achieved with these systems since they are not prone to oxidative addition/reductive elimination chemistry, and ultimately catalytic C-H borylation was developed by the groups of Smith and Hartwig using precious metal systems.[100-103]



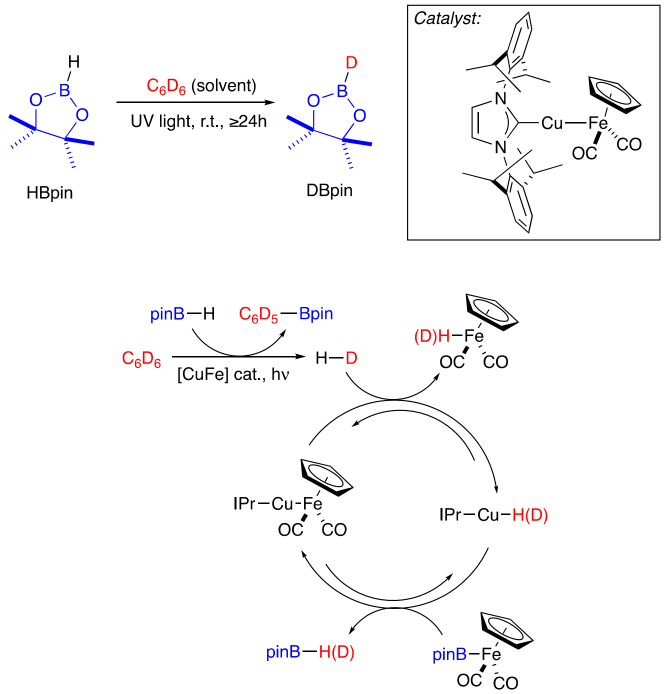
Scheme 6. Stoichiometric C-H borylation mediated by Fe complexes under (a) photochemical and (b) thermal conditions.

Given the relationships between the original $[M_{CO}]$B(OR)$_2$ complexes and the heterobimetallic species being studied by our group, we sought to develop catalytic transformations in which binuclear L_nM-$[M_{CO}]$ bond activation and formation processes could be leveraged to continuously regenerate the active $[M_{CO}]$B(OR)$_2$ species catalytically. Upon investigating several such heterobimetallic catalysts, we reported catalytic C-H borylation of unactivated arenes under UV irradiation conditions with (IPr)Cu-FeCp(CO)$_2$ (Scheme 6).[86] Catalysis required both the Cu and Fe sites to be present, and turnover was not observed with (IPr)CuX, CpFe(CO)$_2$Bpin, or [FeCp(CO)$_2$]$_2$ in place of (IPr)Cu-FeCp(CO)$_2$. Limitations of this initial system include the requirement for solvent quantities of arene substrate, need for induction by UV light, low turnover numbers, and low turnover frequencies. On the other hand, at the time of our report, this system represented the first non-precious metal catalyst for C-H borylation and exhibited the sterically directed site selectivity characteristic of Ir-catalyzed systems. Subsequently, several other groups have pursued non-precious metal catalysts for C-H borylation,[104-108] including an FLP system with cooperative bond activation processes.[109] However, as yet no non-precious metal catalyst for C-H borylation has been reported that enables functionalization of stoichiometric (rather than large excess) quantities of unactivated arenes, whether under thermal or photochemical conditions.



Scheme 7. Catalytic C-H borylation mediated by a Cu/Fe heterobimetallic catalyst.

More importantly to us, this system served as a proof of concept for incorporation into catalytic transformations of binuclear bond activation and formation processes involving (NHC)Cu-$[M_{CO}]$ complexes. According to our proposed mechanism (Scheme 7),[88] bifunctional B-H activation by (IPr)Cu-FeCp(CO)$_2$ generates (IPr)CuH and CpFe(CO)$_2$Bpin reversibly (vide supra). Upon photochemical C-H borylation of the arene substrate by the iron boryl according to Hartwig's σ-bond metathesis mechanism,[110] the protic CpFe(CO)$_2$H intermediate forms. Under stoichiometric Fe conditions, this species was shown to decay to inactive [FeCp(CO)$_2$]$_2$ under UV irradiation.[96] Under catalytic conditions, the protic iron hydride rapidly recombines with hydridic (IPr)CuH to evolve H_2 and regenerate the (IPr)Cu-FeCp(CO)$_2$ catalyst. The H_2 evolution reaction was shown to be quite rapid in stoichiometric reactivity studies,[86] and we propose that it dramatically outcompetes [FeCp(CO)$_2$]$_2$ formation as no trace of this species was detected in *post situ* analysis of the catalyst decomposition mixture.[88] Overall, the role of the [(IPr)Cu]$^+$ partner within the binuclear catalyst is to serve as a hydride shuttle that allows for continuous regeneration of the active FeCp(CO)$_2$Bpin intermediate.

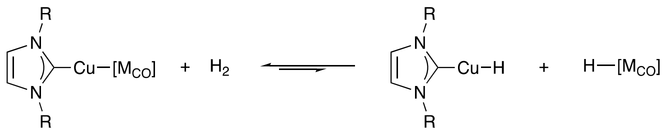


Scheme 8. Hypothetical mechanism for observed H/D scrambling invoking reversible B-H and H-H bond activation/formation.

The key C-H/Fe-B σ-bond metathesis process in these stoichiometric and catalytic Fe-mediated reactions is thought to occur at a vacant Fe coordination site opened by UV-induced CO dissociation.[110] Catalytic C-H borylation under thermal conditions can thus be envisaged if one or more CO ligands from the heterobimetallic photocatalyst is replaced with a thermally labile ligand.[111] Towards this end, we revisited stoichiometric Fe-mediated C-H borylation with a series of CpFe(PR$_3$)$_2$Bpin complexes and disclosed thermal C-H borylation with a sterically hindered CpFe(PEt$_3$)$_2$Bpin derivative (Scheme 6b).[112] However, catalysis was not observed due to the inability of H_2 evolution to occur from reaction between (IPr)CuH and CpFe(PEt$_3$)$_2$H, which is no longer protic in character due to the replacement of withdrawing CO ligands with donating phosphines.[79] Our group is currently in pursuit of a $[M_{CO}]$Bpin system that is sufficiently labile for thermal C-H borylation but that also results in a $[M_{CO}]$H intermediate with enough protic character to participate in the heterobimetallic mechanism shown in Scheme 7.

Semi-hydrogenation of alkynes. During the photochemical boryation of benzene-d_6 with the (IPr)Cu-FeCp(CO)$_2$ catalyst, we observed H/D scrambling of the pinacolborane hydride position during *in situ* NMR monitoring.[86] We assumed that the HD produced initially by borylation of benzene-d_6 by HBpin was reacting with the bimetallic catalyst to produce (IPr)CuD equivalents. Since stoichiometric reactivity experiments had established that (IPr)CuH reacts with $FeCp(CO)_2Bpin$ to produce pinacolborane reversibly (*vide supra*), we hypothesize that the observed H/D scrambling occurs by a mechanism that requires reversible B-H *and* H-H bond activation/formation (Scheme 8). With this realization, we next sought to shift from the dehydrogenative borylation reaction to hydrogenative processes wherein bimetallic H-H cleavage enables H_2 delivery to substrates catalytically. Of course, canonical homogeneous catalysts for hydrogenation reactions involve single-site systems of precious metals such as Ru, Rh, or Ir. The targeted heterobimetallic hydrogenation chemistry would add to the toolbox of cooperative strategies for catalytic H_2 activation and delivery.[2]

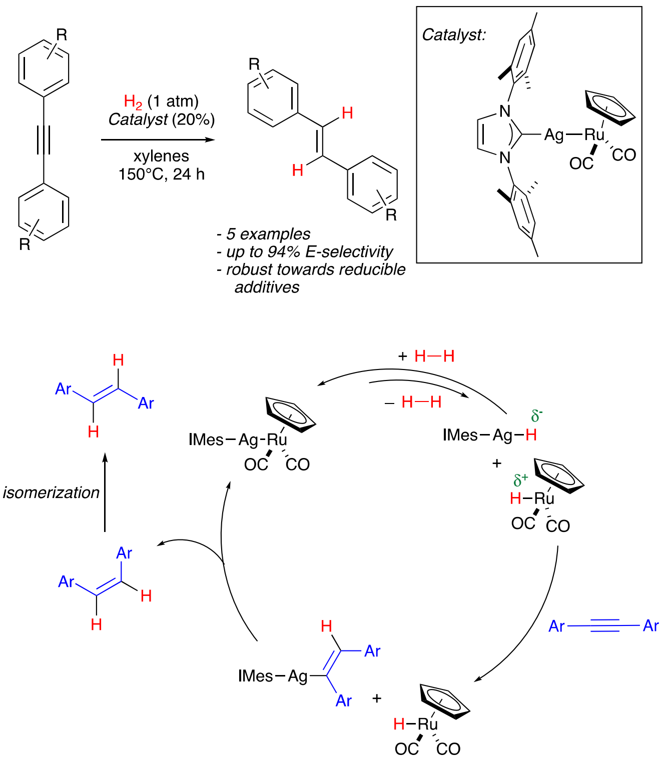
Table 1. Correlation of catalyst hydrogenation and $H[M_{CO}]$ pK_a



$[M_{CO}]$	ΔG_{298K} of H_2 activation[a]	pK_a of $H[M_{CO}]$[b]
$RuCp(CO)_2$	20.1	25
$FeCp(CO)_2$	21.9	23
$WCp(CO)_3$	24.8	18
$Mn(CO)_5$	33.0	14
$MoCp(CO)_3$	34.0	17
$CrCp(CO)_3$	34.5	16
$Co(CO)_4$	49.0	12

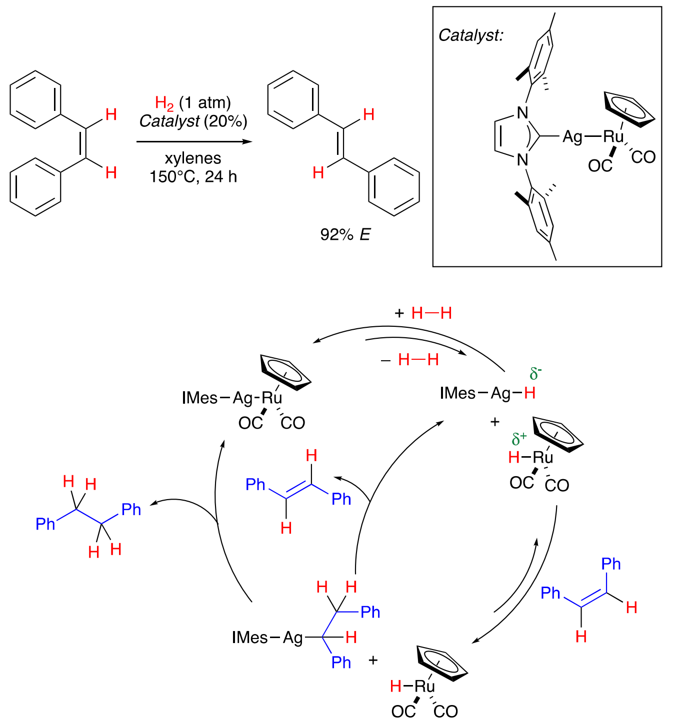
[a]From DFT calculations.[85] [b]From ligand acidity constants in CH_3CN.[79,80]

When commencing the study of H_2 activation, DFT calculations were used to guide catalyst screening.[85] The position of the hydrogenation/dehydrogenation equilibrium for (NHC)Cu-$[M_{CO}]$ complexes was calculated to correlate roughly with pK_a of the corresponding $[M_{CO}]H$ complexes (Table 1), consistent with the role of the $[M_{CO}]^-$ fragment to act as a proton shuttle in FLP-like catalytic hydrogenation processes.[20] Thus, the most promising $[M_{CO}]$ candidates were identified as $[FeCp(CO)_2]$ and $[RuCp(CO)_2]$. Additionally, the H_2 cleavage reaction was found to be more favourable for a (NHC)Ag-$RuCp(CO)_2$ model than its (NHC)Cu-$RuCp(CO)_2$ analogue by an additional ~6 kcal/mol.



Scheme 9. Catalytic alkyne semi-hydrogenation mediated by a Ag/Ru heterobimetallic catalyst.

Delivery of H_2 to diphenylacetylene was chosen as a model reaction for initial screening, as (NHC)CuH intermediates are known to readily insert alkyne substrates.[113] Catalyst screening results were generally consistent with the computational analysis of H_2 cleavage thermodynamics: while diphenylacetylene reduction was observed with several (NHC)M-M'$Cp(CO)_2$ catalysts (M = Cu or Ag, M' = Fe or Ru), the highest conversions were noted for derivatives with M = Ag and M' = Ru.[85] Optimized conditions allowed for complete consumption of the alkyne starting material with catalytic (IMes)Ag-$RuCp(CO)_2$ (20%) under H_2 (1 atm) at 150°C (Scheme 9). To our surprise, the major product from diphenylacetylene reduction was not *Z*-stilbene (as expected) or 1,2-diphenylethane but rather *E*-stilbene. This *trans*-selective semi-hydrogenation behaviour was observed for other diarylalkyne substrates, and additive tests[114] indicated that the process was highly chemoselective for alkyne reduction in the presence of many other functional groups including ketones, nitriles, esters, alkenes, and alkyl chlorides. Alkyl substitution on the alkyne moiety was not tolerated due to chain walking isomerization. The catalytic results were noteworthy not only because of the unusual bimetallic H_2 activation but also because *trans*-selective semi-hydrogenation catalysts that use H_2 as the terminal reductant are exceedingly rare.[115-121]



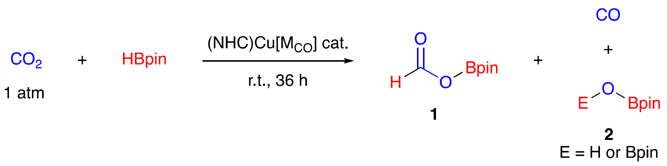
Scheme 10. Catalytic stilbene isomerization mediated by a Ag/Ru heterobimetallic catalyst under semi-hydrogenation conditions.

Our expectation for *cis*-selective semi-hydrogenation behaviour in this system was based on the known *syn*-hydrocupration reactivity of (IPr)CuH and other copper hydrides.[113,122] Thus, we hypothesized that under catalytic conditions, *Z*-stilbene isomers were forming initially and then were being isomerized to the *E*-stilbenes. Consistent with this proposal, the parent *Z*-stilbene was found to isomerize under the catalytic conditions to *E*-stilbene quantitatively.[85] This isomerization chemistry required both the bimetallic catalyst and H_2 to be present to be kinetically competent, suggesting metal-hydride mediated isomerization. We proposed isomerization by migratory insertion and β-hydride elimination of the *Z*-stilbene to produce *E*-stilbene under thermodynamic control (Scheme 10). Evidence for this proposal includes formation of trace quantities of the fully reduced alkane product in all product mixtures, consistent with the intermediacy of a metal alkyl species. According to this proposal, selectivity for alkene products over alkane products is under kinetic control, dictated by the metal alkyl intermediate undergoing unimolecular β-hydride elimination more rapidly than bimolecular alkane elimination.[92] However, it should be noted that further studies on the mechanism of *trans*-hydrogenation are underway. Caution is necessary because the initial mechanistic proposals are built on stereochemistry of known alkyne reactivity with copper hydride species; discrete silver hydride analogues have not been studied before with regard to alkyne migratory insertion,[123] and a (NHC)AuH analogue is known to mediate *anti*-hydroauration of activated alkyne systems.[124]

Orthogonal mononuclear catalysis

Deoxygenation of CO_2 by tandem catalysis. Our first example of orthogonal co-catalysis with mononuclear species emerged from studies of B-H activation. When establishing the B-H activation/formation equilibrium shown in Scheme 4a, one key observation involved driving the equilibrium in the B-H activation direction by capturing (IPr)CuH with CO_2.[86] Our expectation was that CO_2 insertion would yield (IPr)CuO_2CH, which in turn would extrude HCO_2Bpin (**1**) upon exposure to excess HBpin as was established previously.[125] Indeed, (NHC)CuH catalysis for reduction of CO_2 by silane and borane reductants, [E]-H where [E] = silyl or boryl, is known to produce HCO_2[E] products quantitatively and selectively.[125-127] In reality, we observed formation not only of **1** but also of [E]OBpin (**2**; [E] = H or Bpin), the latter resulting from CO_2 deoxygenation. This result was validated under catalytic conditions; in fact the **1**:**2** ratio, i.e. the formate:CO selectivity, could be controlled by tuning the (NHC)Cu-$[M_{CO}]$ catalyst (Table 2).[128] Catalytic CO_2 deoxygenation was found to require the presence of both metal sites and was favoured for small NHC ligands and for electron-deficient $[M_{CO}]^-$ species.

Table 2. Catalyst control of CO_2 reduction selectivity

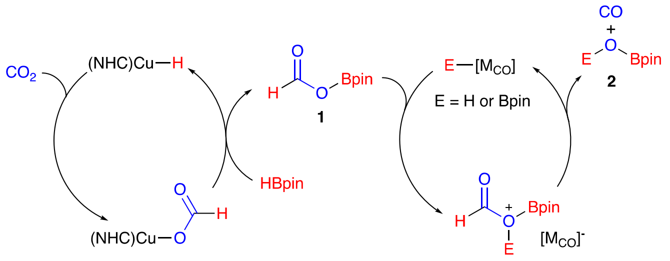


Catalyst	pK_a of H$[M_{CO}]^a$	HBpin conversion (%)	2:1
(IPr)CuFeCp$(CO)_2$	23	72	0.7:1
(IPr)CuWCp$(CO)_3$	18	76	2:1
(IPr)CuMoCp$(CO)_3$	17	73	12:1
(IMes)CuFeCp$(CO)_2$	23	92	>20:1

[a]From ligand acidity constants in CH_3CN.[79,80]

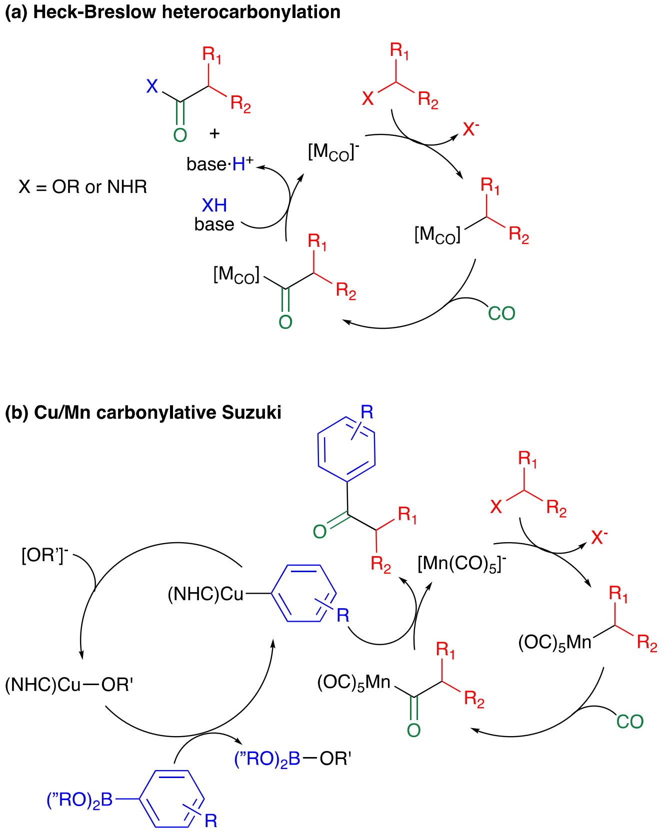
The observation of CO_2 deoxygenation had not been observed previously from [E]-H reductants but instead required the diborane reductant B_2pin_2 in the presence of a (NHC)CuBpin catalyst.[129] In our case, we found that (IPr)Cu-$[M_{CO}]$ complexes were inert towards CO_2 activation,[83] unlike their early transition metal analogues,[36,38,130] thus ruling out a pathway involving binuclear CO_2 activation. We also found that the CpFe$(CO)_2$Bpin component was inert towards the starting materials CO_2 and HBpin independently. Thus, we hypothesized that in our reaction **1** formed from known (IPr)CuH catalysis,[125] while **2** formed from orthogonal tandem catalysis involving (IPr)CuH and $[M_{CO}]$Bpin (Scheme 11). Indeed, subsequent experiments found that while

$CpFe(CO)_2Bpin$ is inert towards CO_2 activation, it does mediate decarbonylation of **1** under the catalytic conditions, consistent with **1** being an intermediate in a tandem process.[128] Overall, the mutually orthogonal roles of the two catalyst components are for $[(NHC)Cu]^+$ to reduce one of the C=O bonds of CO_2 and for $[M_{CO}]^-$ to facilitate C-O cleavage, while bimetallic (NHC)Cu-$[M_{CO}]$ is a dormant off-cycle species.



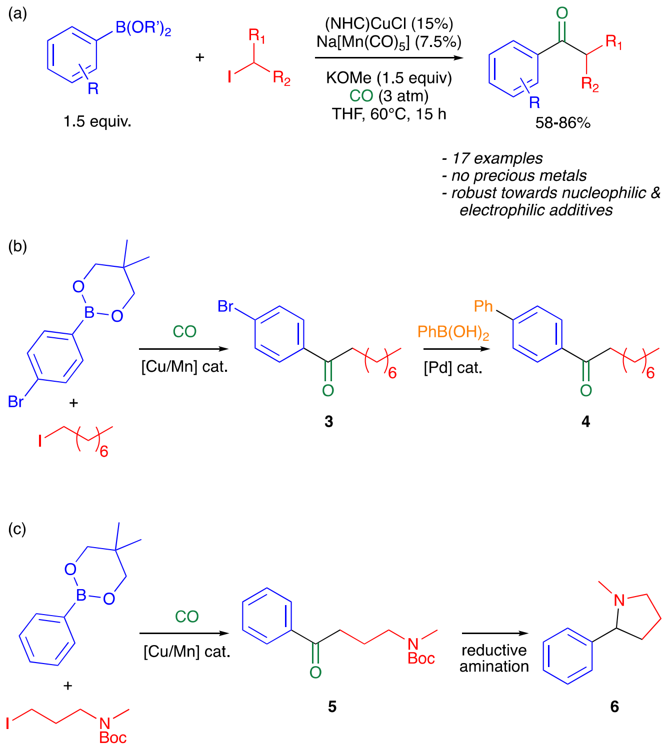
Scheme 11. Catalytic CO_2 deoxygenation by orthogonal tandem catalysis.

Carbonylative C-C coupling by co-dependent bimetallic catalysis. Given the preponderance of carbonyl ligands in the bimetallic catalysts being investigated by our group, we became motivated to pursue novel carbonylative coupling reactions with bimetallic mechanisms. Carbonylative coupling catalysis has established importance for bulk chemical synthesis and also has been applied towards constructing fine chemicals and pharmaceuticals.[131] Early examples of hydroformylation and other catalytic carbonylation reactions utilized non-precious metal systems such as cobalt carbonyl catalysts.[132] In fact, Heck and Breslow utilized the title $[M_{CO}]^-$ species such as $[Co(CO)_4]^-$ and $[Mn(CO)_5]^-$ to catalyse alkoxycarbonylation and aminocarbonylation reactions of alkyl halides as early as 1963,[133] and recent work by Alexanian has advanced such reactions to the point of synthetic utility.[134-136] However, precious metal systems have generally found more favour industrially, largely due to their impressive efficiency and robustness. Hydroformylation reactions often employ Rh catalysts, while carbonylative C-X and C-C cross-coupling reactions typically utilize Pd.[131,137-140] Included among Pd-catalyzed carbonylations are carbonylative C-C cross-coupling reactions to synthesize ketone products, such as carbonylative Heck, Sonogashira, Suzuki, and Negishi variants. In general, these Pd-catalyzed transformations are effective for C(sp^2)-hybridized coupling partners but are intolerant of unactivated C(sp^3)-hybridized coupling partners that can potentially undergo β-hydride elimination under the conditions that allow for carbonylation to occur. The few examples of Pd-catalyzed carbonylative coupling that employ C(sp^3)-hybridized partners tend to have drawbacks including limited scope in some cases,[141] the need for photoirradiation to activate C(sp^3)-X bonds, and the requirement for high CO pressures exceeding 40 atm.[142]



Scheme 12. Carbonylative coupling reactions: (a) Heck-Breslow alkoxy- and aminocarbonylation of alkyl halides, (b) carbonylative Suzuki coupling with alkyl halides catalysed by co-dependent Cu and Mn catalysts.

We viewed carbonylative C-C coupling with non-precious metal systems, which had not been developed prior to our work, as a complementary approach to Pd-catalyzed carbonylation for discovering systems effective for C(sp^3)-hybridized coupling partners under mild conditions. The Heck-Breslow carbonylative C-X coupling reactions[133] provided a mechanistic starting point. The pathway for these reactions (Scheme 12a) involves alkylation of the anionic $[M_{CO}]^-$ catalyst, carbonylation of the metal-alkyl intermediate, and then nucleophilic attack on the resulting metal-acyl intermediate by an alcohol or amine. The general use of carbon nucleophiles to generate ketones was not known for such systems, presumably because many carbon nucleophiles would not only attack the metal-acyl intermediate but also attack the desired ketone product. We hypothesized that organocopper nucleophiles would be appropriate due to their sluggishness towards addition to ketone groups.[143] We furthermore proposed that the key organocopper nucleophiles could be continuously generated in catalytic quantities through transmetalation from stoichiometric arylboronic acid derivatives. The resulting co-dependent catalytic cycles, ultimately developed by us[89] with $[(NHC)Cu]^+/[Mn(CO)_5]^-$ co-catalysts (Scheme 12b), would thus resemble dual Cu/Pd chemistry that has its roots in the work of Sonogashira[144] and has been developed recently by Semba/Nakao,[66,145] Brown,[65] and others.[63] Moreover, the net bimetallic carbonylative Suzuki coupling reaction would complement Ryu's Pd-catalysed carbonylative Suzuki reactions with alkyl iodide electrophiles that operate at high CO pressure with requirement of photoirradiation.[146] Notably, the orthogonal behaviour of the two mononuclear co-catalysts here are co-dependent; in other words, each cycle is inoperative in the absence of the other, which is distinct from the tandem catalysis described above for CO_2 deoxygenation.

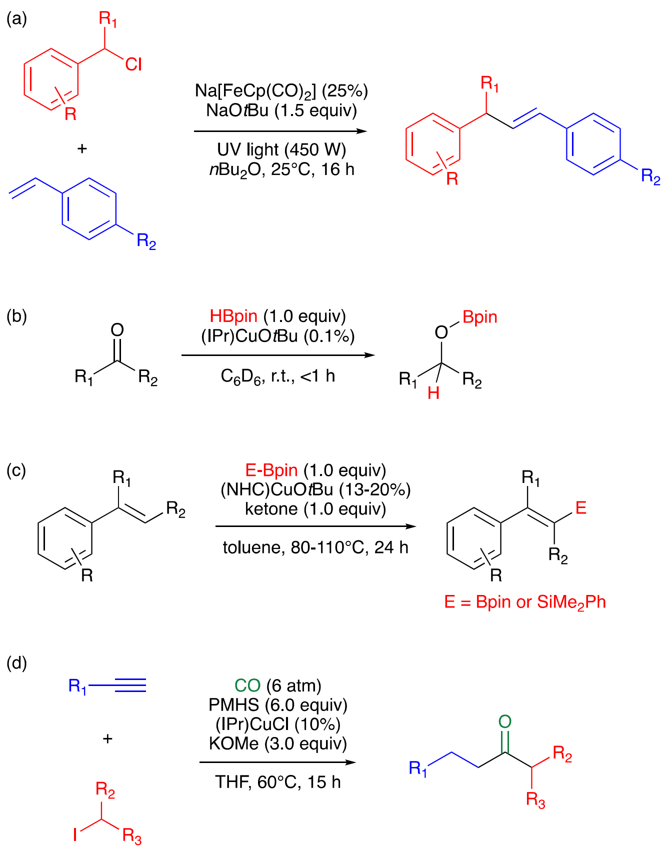


Scheme 13. Cu/Mn co-catalyzed carbonylative Suzuki coupling: (a) optimized conditions, (b) complementarity to Pd catalysis, (c) application towards N-heterocycle synthesis.

Our optimized Cu/Mn co-catalyzed reaction conditions are comparatively mild in the context of carbonylation catalysis, operating at 60°C with low CO pressure (3 atm).[89] The carbonylative Suzuki coupling reaction works well with a range of electron-rich, electron-poor, and sterically hindered aryl boronic ester nucleophiles (Scheme 13a). Primary and secondary alkyl iodides react efficiently, and alkyl bromides and tosylates can be used in the presence of stoichiometric tetrabutylammonium iodide. Additive tests[114] indicate that the reaction is robust towards electrophilic functional groups (e.g. aldehydes, esters, nitriles), nucleophilic functional groups (e.g. primary amine, alcohol), and some heterocycles. Due to the radical mechanism for alkyl iodide activation by $[Mn(CO)_5]^-$,[147] the Cu/Mn co-catalyzed conditions are complementary to Pd-catalyzed conditions with chemoselectivity towards alkyl iodide activation in the presence of aryl halide functional groups. This behaviour was highlighted by the synthesis by Cu/Mn co-catalyzed carbonylation of ketone **3**, which has an aryl bromide handle that was further elaborated using classical Pd-catalyzed Suzuki coupling to generate biarylketone **4** (Scheme 13b). The robustness of the coupling reaction towards amino groups allowed us to generate ketone **5** *in situ* and convert it without purification to pyrrolidine **6** by classical reductive amination (Scheme 13c). Lastly, mechanistic experiments established that metal-metal bonded (NHC)Cu-$Mn(CO)_5$ catalysts are not viable on-cycle species for this transformation, and that the proposed heterobimetallic ketone-forming C-C coupling reaction between arylcopper and acylmanganese partners is viable under the catalytic conditions.

Serendipitous discoveries

In all the cases described thus far, it was established through control experiments that both $[(NHC)M]^+$ and $[M_{CO}]^-$ metal sites were necessary for the observed catalytic behaviour. This requirement stems from the various bimetallic reaction pathways that, while mechanistically diverse, all require some manner of communication between the two metal sites despite their being spatially separated for much or all of the transformation. Of course, we also have discovered many cases where the two metal sites do not communicate, but rather the co-catalysts separate and then one or the other acts simply as an inert spectator. These instances have become apparent when control experiments establish that the presence of both metal sites is *not* a requirement for catalysis. A subset of these cases has led us to discover unknown modes of monometallic catalysis serendipitously. For example, early in our studies we found that $[FeCp(CO)_2]^-$ itself is able to catalyse photochemical Heck coupling reactions between styrenes and benzyl halides (Scheme 14a).[148]
More commonly, serendipitous discoveries of copper-carbene catalysis[149] have emerged from our approach. In studies related to bimetallic CO_2 hydroboration, we found that (IPr)CuO*t*Bu is an unusually efficient catalyst for hydroboration of ketones and aldehydes (Scheme 14b).[150] In studies related to bimetallic C-H borylation, we found that (NHC)CuO*t*Bu catalysts can be used in the presence of sacrificial ketone oxidants for dehydrogenative borylation and silylation of styrenes (Scheme 14c).[151] Finally, in studies related to bimetallic carbonylative coupling, we found that copper-carbenes are able to catalyse hydrocarbonylative C-C coupling reactions that combine alkynes and alkyl iodides under reductive carbonylation conditions to produce dialkylketones (Scheme 14d).[152]



Scheme 14. Serendipitous discoveries of monometallic catalysis: (a) Fe-catalyzed Heck benzylation, and Cu-catalyzed (b) ketone hydroboration, (c) dehydrogenative styrene borylation/silylation, (d) hydrocarbonylative C-C coupling of alkynes and alkyl iodides.

Collectively, these serendipitous discoveries demonstrate the advantages of studying cooperative chemistry using components that individually have their own interesting reaction chemistry, of conducting proper control experiments, and of following up on unexpected leads resulting from what might otherwise be considered “failed” studies in relation to the main catalytic concept being pursued.

Conclusions

It stands to reason that a tremendous amount of chemical reactivity space accessible using innovative catalyst design strategies remains to be explored by catalysis science. The heterobimetallic chemistry featured here is one of many such strategies employing cooperativity and multi-site reactivity, all of which complement the traditional single-site homogeneous catalysis approach. This feature provides an account of our group’s efforts to develop bimetallic catalysis using pairs of Lewis acidic copper carbenes and Lewis basic metal carbonyls. From a conserved (NHC)Cu-[M_{CO}] design, catalytic transformations spanning a diverse range of catalytic mechanisms emerged, including reactions that operate using binuclear bond activation/formation processes, orthogonal tandem catalysis of mononuclear co-catalysts, and orthogonal co-dependent catalysis of mononuclear co-catalysts. This mechanistic diversity is possible due to the dynamic nature of the catalysts in solution that equilibrates heterobinuclear species with charge-separated “frustrated” Lewis acid/base pairs, thus allowing catalysis to proceed through the productive member of the equilibrium speciation under a given set of reaction conditions.

For this particular system, the cooperative behaviour of the catalysts enabled non-precious metal systems for C-B and C-C coupling reactions and modulated product selectivity in reductions of unsaturated substrates. Reactivity and selectivity was found to correlate with thermodynamic parameters of the metal-carbonyl anion component of the catalyst, thus providing a rational basis for predicting catalytic behaviour. The curiosity-based approach to catalyst discovery in some cases led to unanticipated positive results, such as unusual *trans*-selectivity for alkyne semi-hydrogenation, and also gave rise to a range of unexpected yet useful transformations catalysed by copper-carbenes alone. These initial results provide the mechanistic roadmaps for future reaction discovery with these and related heterobimetallic Lewis acid/base pairs. Indeed, we believe we are only “touching the tip of the iceberg” regarding catalytic reaction discovery with such systems. In particular, we anticipate tremendous growth in accessible transformations as new types of X-Y bonds are approached using binuclear bond activation, as new reaction partners are introduced into the orthogonal mononuclear catalysis motifs, and as new types of Lewis acidic co-catalyst are introduced into the L_nM-[M_{CO}] design in place of copper carbenes that we used initially. In summary, we assert that this system stands a prominent case study showcasing the value of pursuing unconventional catalyst design strategies from a fundamental scientific standpoint.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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