Non-Precious Metal Catalysts for C–H Borylation Enabled by Metal–Metal Cooperativity

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Abstract: Homogeneous catalysts for C–H functionalization typically require precious metals such as Pd, Ru, Rh, or Ir because of their facility in mediating two-electron redox mechanisms. Base metals such as Cu or Fe instead tend to undergo one-electron redox processes. By coupling together two base metal sites in a hetero-bimetallic catalyst design, base metal catalysts for photochemical C–H borylation were discovered. The optimal catalyst, (IPr)Cu–FeCp(CO)$_2$, represents the first homogeneous catalyst for C–H borylation that contains no precious metals. Using metal–metal cooperativity in this way allows for base metal catalysts to replace precious metal catalysts while maintaining advantageous regioselectivity patterns. The proposed mechanism for heterobimetallic C–H borylation features bimetallic versions of classic organometallic reaction steps, serves as a guide for future catalyst designs, and opens the possibility for other precious metal transformations to be approached using metal–metal cooperativity as a design strategy.

Key words: boron, carbene complexes, copper, homogeneous catalysis, iron

1 Introduction

Human beings have been able to functionalize C–H bonds in organic matter since the invention by *Homo erectus* of controlled fire. Selective functionalization of C–H bonds in complex organic molecules, however, is a much more difficult technological advance enabled more recently by chemical catalysis.[1] Any catalysts for C–H functionalization that operate by single-electron redox steps, including most heterogeneous catalysts for C–H oxidation, have inherent limitations on selectivity because relative rates of C–H activation are dictated by C–H bond strengths alone,[2] much like in the combustion reaction of a fire. On the other hand, homogeneous systems enable selectivity due to the range of two-electron redox mechanisms available for bond-breaking and bond-forming events that are facilitated when the catalyst's metal and its ligand set are chosen judiciously.[3] In this regard, precious metals have been particularly important historically due to their propensity to undergo two-electron redox processes, in contrast to non-precious metals, which tend to mediate one-electron redox processes (Scheme 1).[4]

Several catalytic technologies for selective C–H bond functionalization that rely on directing groups have been developed, typically using homogeneous precious metal

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catalysts containing Pd[5] or Rh[6]. In terms of selective C–H bond functionalization that does not rely on built-in directing groups, the most prominent technology is C–H borylation,[7] wherein an unactivated alkane or arene C–H bond is converted directly to a C–B bond. In part because the borylated products are versatile synthetic building blocks, C–H borylation has become one of the most important inventions in homogeneous catalysis over the last 20 years. Catalytic C–H borylation typically relies on precious metals such as Rh or Ir, which are among the least abundant and most expensive elements in the transition series. These heavy metals also are significantly more toxic than the lighter 3d metals, which is an important consideration for potential pharmaceutical and biomedical applications. A more sustainable and less economically volatile approach would be to use non-precious metal catalysts containing only earth-abundant elements.[8] However, doing so would require overcoming the inherent preference of base metals, for example Cu or Fe, to undergo one-electron redox transformations (Scheme 1), for example Cu(II)/Cu(I) or Fe(III)/Fe(II).[4] Understanding the fundamental science necessary to control these propensities has important implications across many fields that rely on catalysis, including alternative energy conversion, where it is not reasonable to expect precious metals to be viable on a global scale.[8,9]
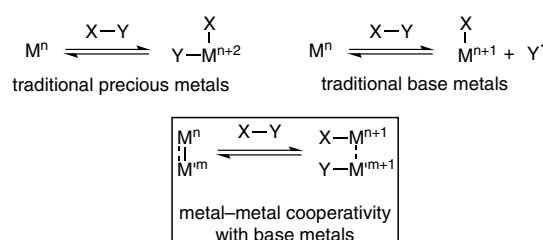
Scheme 1 Multielectron redox processes at single-site precious metal, single-site base metal, and base metal heterobimetallic cores

Several design strategies have been advanced for inducing base metals to mimic the two-electron redox chemistry of precious metals.[10,11] For example, coupling the one-electron redox manifold of a base metal with the chemistry of a non-innocent ligand residue has led to recent discoveries of base metal catalysts for hydrogenation[12] and dehydrogenation[13] reactions that otherwise would require precious metal catalysts. Similarly, hydrogenation reactions have been catalyzed recently by p-block nucleophile/electrophile pairs ('frustrated Lewis pairs') that mimic the hydrogenation chemistry of precious d-block metal systems.[14] Applications of these design strategies outside the realm of hydrogenation and dehydrogenation reactions have yet to emerge.

An alternative design strategy involves coupling the individual one-electron redox manifolds of two base metals in order to mediate net two-electron redox processes during catalysis (Scheme 1). Although the use of such metal–metal cooperativity in catalytic scenarios is important for some precious metal systems involving Pd_2,[15] Rh_2,[16] Au_2,[17] or Ag_2[18] intermediates, the use of this design strategy for base metal catalysis is only beginning to emerge as a general concept[19] despite a recent renaissance in the synthesis of bimetallic complexes featuring earth-abundant metals.[20] In this context, our group recently developed the syntheses of Cu–Fe and Zn–Fe heterobimetallic complexes supported by N-heterocyclic carbene (NHC) ligands and featuring the Fp fragment [Fp = $FeCp(CO)_2$].[21,22] We hypothesized that these complexes would be good candidates for replacing precious metals in catalytic C–H borylation,[23] as will be described in this article.

2   Brief History of C–H Borylation

The C–H borylation reaction was first discovered as a stoichiometric transformation involving earth-abundant metals activated under photochemical conditions. In 1995, Hartwig and co-workers disclosed that the boryliron complex FpBcat (cat = catecholate) could quantitatively convert arene substrates to arylboronate esters under UV irradiation conditions (Scheme 2).[24] One can imagine the by-product of this reaction, FpH, closing a catalytic cycle by reacting with HBcat to regenerate FpBcat. Such a transformation likely would involve a two-electron redox pathway, such as an oxidative addition/reductive elimina-

tion sequence, that would be uncommon for a single-site Fe system. Instead, under the reaction conditions, FpH rapidly converted to inactive Fp_2 through loss of H_2, which is a one-electron redox process per Fe center. Similar stoichiometric C–H borylation was later developed for alkane substrates using $Cp*W(CO)_3Bcat'$ (cat' = 3,5-dimethylcatecholate).[25]
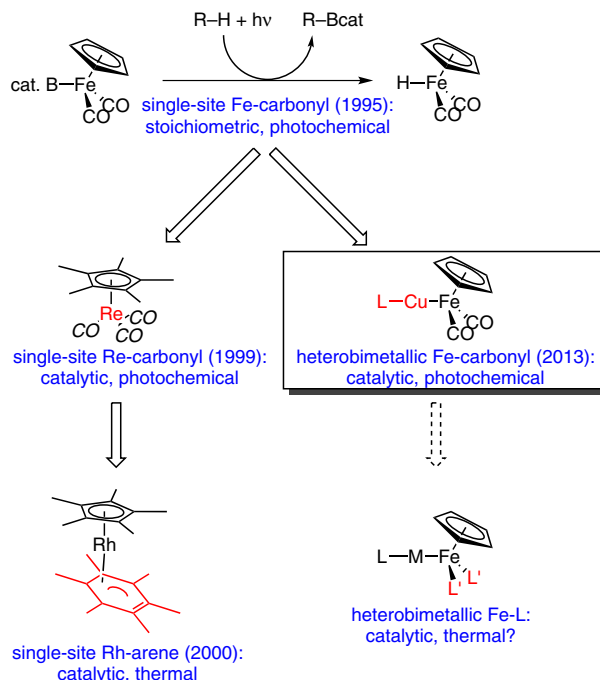
Scheme 2 Evolution of C–H borylation catalysis, starting from the initial discovery of stoichiometric Fe-mediated C–H borylation and proceeding to subsequent catalyst designs based on single-site precious metals as well as base metal heterobimetallics (this work). See references 7 and 23–31.

Conventional wisdom dictates that in order to leverage stoichiometric chemistry into catalytic chemistry, one should shift focus from base metals like Fe to precious metals, where two-electron redox pathways are available and might lead to catalytic turnover. Indeed, Hartwig and co-workers disclosed in 1999 a report of catalytic C–H borylation by using a half-sandwich complex, $Cp*Re(CO)_3$,[26] that was closely related to the original Fp system in overall structure but featured the precious metal, Re, instead of the base metal, Fe. Because of the presence of CO ligands, UV irradiation was still required for catalysis and represented a practical limitation. Iverson and Smith had recently reported the first demonstration of catalytic C–H borylation, which utilized CO-free Ir half-sandwich complex under thermal conditions but lacked catalytic efficiency.[27] The groups of Hartwig and Smith subsequently utilized the CO-free half-sandwich complex $Cp*Rh(\eta^4\text{-}C_6Me_6)$, which features a thermally labile π-arene ligand instead of photochemically labile CO ligands, for catalytic borylation under thermal conditions of alkanes[28] and arenes,[29] respectively (Scheme 2). After further contributions from Hartwig, Smith, Ishiyama,

Miyaura, Maleczka, and others, the current state-of-the-art catalysts feature Ir ligated by either phosphines[30] or bipyridines,[31] are able to catalyze arene C–H borylation under mild conditions, and have widespread use for constructing arylboronate esters as synthetic building blocks for various applications.[7]

3   Heterobimetallic Paradigm for C–H Borylation

Our group's central hypothesis is that, contrary to conventional wisdom, catalysis can be achieved with base metals in many cases by using metal–metal cooperativity to replace single-site precious metal systems (Scheme 1). Because the heterobimetallic Cu–Fe and Zn–Fe complexes being synthesized in our group[21] happened to feature the same Fp fragment utilized in the original stoichiometric boryliron studies by Hartwig and co-workers,[24] C–H borylation catalysis provided a natural testing ground for our hypothesis (Scheme 2).[23]

Using HBpin (pin = pinacolate) as a borylating reagent and benzene-d_6 as a test substrate and solvent, we replicated the photochemical reaction conditions for stoichiometric Fe-mediated C–H borylation,[24] but replaced stoichiometric FpBcat with catalytic amounts of various Cu–Fp and Zn–Fp heterobimetallic complexes. One complex in particular, (IPr)CuFp [IPr = N,N'-bis(2,6-diisopropylphenyl)imidazol-2-ylidene], exhibited superior performance as a catalyst. Even at catalyst loadings of 5 mol%, (IPr)CuFp was able to produce C_6D_5Bpin in yields exceeding 70%. Furthermore, this catalyst was highly robust and exhibited only modest decrease in catalytic efficiency during consecutive usage. To the best of our knowledge, (IPr)CuFp represents the first homogeneous catalyst for C–H borylation that does not require any precious metal resources,[32] as we communicated recently (Scheme 3).[23]
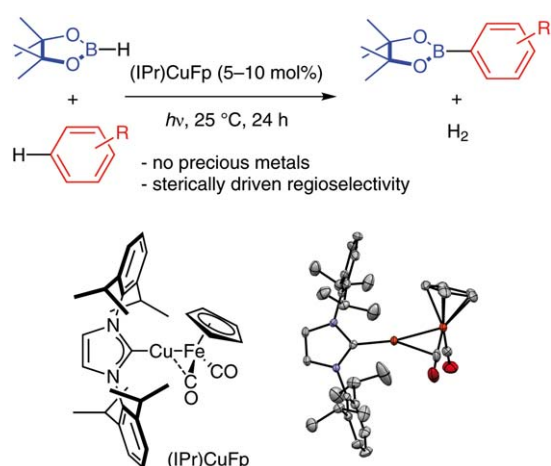

Scheme 3 (*top*) Borylation of arene C–H bonds catalyzed by base metal heterobimetallic complexes; (*bottom*) line drawing and X-ray crystal structure of the optimal catalyst, (IPr)CuFp. See references 21 and 23.

Importantly, the monometallic fragments that compose this heterobimetallic catalyst were tested and did not show catalytic activity under the same conditions. For example, catalytic C–H borylation of benzene-d_6 was not observed when using (IPr)CuCl, K^+Fp^-, or FpBpin in place of (IPr)CuFp. The homobimetallic species, Fp_2, also did not catalyze the reaction. Clearly, therefore, the presence of a heterobimetallic catalyst with a polar metal–metal bond is necessary to catalyze C–H borylation in the absence of precious metals. Although there are many examples of metal–metal interactions enhancing reactivity and/or selectivity in homogeneous catalysis,[33] it is rare for catalytic reactions to require metal–metal interactions as this one does.

A collection of arene substrates in addition to benzene also were tested for photocatalytic C–H borylation by (IPr)CuFp.[23] Yields in some cases approached quantitative conversion. Through examination of monosubstituted and disubstituted arene substrates, we established that regioselectivity for C–H borylation by (IPr)CuFp is dictated by steric rather than electronic factors. This phenomenon is completely analogous to behavior of the classical precious metal catalysts for C–H borylation,[7] indicating that transitioning from single-site precious metal catalysts to base metal heterobimetallic catalysts does not adversely affect the regioselectivity patterns that have made catalytic C–H borylation so useful. A particularly instructive example is 1,3-dimethylbenzene, which underwent C–H borylation exclusively at the 5-position, the most sterically accessible position but the least reactive position under standard electrophilic aromatic substitution conditions.

A proposed mechanism for heterobimetallic C–H borylation, supported by our stoichiometric reactivity studies,[23] features bimetallic versions of classic organometallic reactions that are typically observed at single metal centers (Scheme 4). Initially, (IPr)CuFp undergoes bimetallic oxidative addition with HBpin, producing (IPr)CuH and FpBpin as the immediate products. (IPr)CuH is a known species that has been characterized previously by Sadighi and co-workers as a hydride-bridged dimer in the solid state,[34] and FpBpin is closely related to Hartwig's original FpBcat complex.[24] Our reactivity studies[23] clearly indicate that the B–H bimetallic oxidative addition with (IPr)CuFp, though feasible at room temperature, is reversible and favors the reactants side of the equilibrium. The FpBpin intermediate, when produced in small concentrations by reversible B–H activation, is expected to mediate photochemical C–H borylation in a manner akin to the reactivity observed previously for FpBcat.[24] Upon photochemical C–H borylation, FpH is produced as a catalytic intermediate. In the stoichiometric Fe chemistry, FpH rapidly decomposes to inactive Fp_2 under the reaction conditions. In the heterobimetallic regime, however, FpH is efficiently trapped by the (IPr)CuH dimer to liberate H_2 via bimetallic reductive elimination and regenerate (IPr)CuFp for further reaction. Our independent reactivity studies[23] showed that this bimetallic reductive elimination step is highly clean and efficient at room temperature and

does not require photochemical activation. The presence of a heterobimetallic catalyst, then, facilitates two processes that together render the previously stoichiometric Fe chemistry catalytic. First, the polar Cu–Fe bond reversibly activates HBpin, a transformation that cannot happen in the absence of Cu. Secondly, FpH is rapidly trapped before converting to Fp_2, an inactive species that was never observed even in trace quantities in any of our catalytic reaction mixtures.
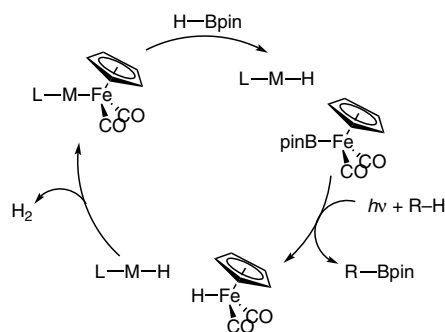
Scheme 4 Proposed mechanism for photochemical C–H borylation catalyzed by base metal heterobimetallic M–Fp complexes. See reference 23.

4   Future Outlook

One crucial point about the proposed heterobimetallic mechanism is that only the C–H borylation step requires photochemical activation; the B–H oxidative addition and H–H reductive elimination steps proceed readily at room temperature without UV irradiation. The need for UV irradiation is a practical limitation of the new technology, and so this mechanistic insight provides a guide for how to overcome this limitation. Studies by Hartwig and coworkers have established the mechanism of stoichiometric C–H borylation by FpBcat.[24] Dissociation of a CO ligand induced by UV irradiation reveals an unsaturated, 16-electron intermediate, and then C–H functionalization occurs at the vacant coordination site. The path to developing base metal catalysts for C–H borylation, then, would likely involve designing catalysts related to (IPr)CuFp but where the CO ligands on Fe have been replaced with thermally labile ligands (Scheme 2). Anionic $[CpFeL_2]^-$ fragments of this type already exist and provide excellent candidates for future heterobimetallic catalyst development.[35] It is noteworthy that this approach closely mimics the history of precious metal-catalyzed C–H borylation,[7] where initial catalysts required photochemical conditions and then thermal conditions were developed by shifting to CO-free analogues (*vide supra*). Indeed, only when the requirement for UV irradiation is removed can the base metal catalysts described here be considered direct competitors with their precious metal counterparts.

A second crucial point about the proposed catalytic mechanism is that the two steps which are enabled by the heterobimetallic design strategy can be viewed as bimetallic oxidative addition and bimetallic reductive elimination: in

other words, bimetallic analogues of classical organometallic two-electron redox processes that typically occur at single metal centers. Assuming this point of view is valid, it opens the possibility of using metal–metal cooperativity to approach other problems in catalysis that typically require precious metal resources and proceed through canonical oxidative addition/reductive elimination sequences. Especially as emerging problems of massive scale including alternative energy conversion and storage grow to rely on catalytic technologies,[9] such fundamental studies towards replacing precious metals with base metals will continue to gain importance, in our view.

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