Inner- and outer-sphere cross-coupling of high F_{sp3} fragments

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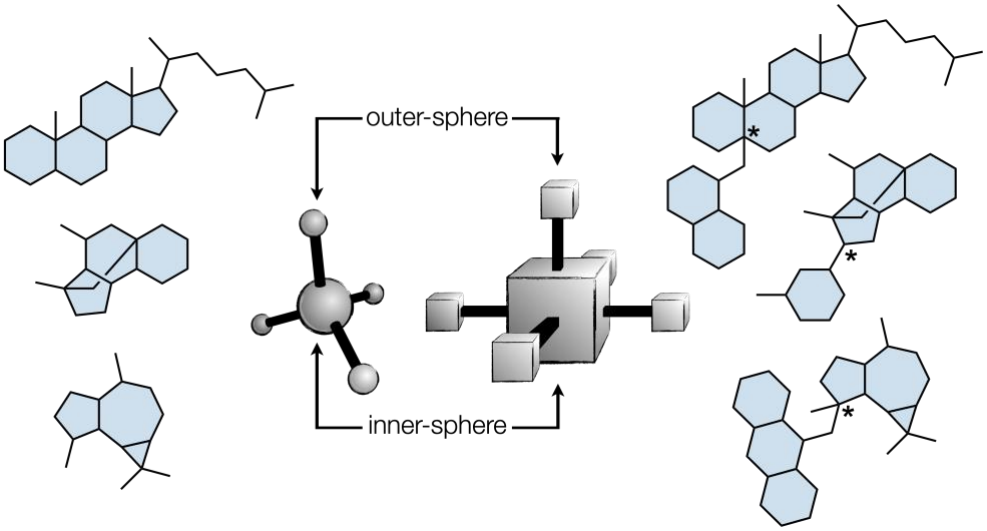

CONSPECTUS: Natural products research derives from a desire to explore, understand, and perturb biological function with atomic precision. To reach these goals at all, let alone efficiently, requires thoughtful, strategic, and creative problem solving. Often this means bold and unprecedented disconnections that would simplify access, if only the methods existed to bridge these theoretical gaps. Whereas biological interrogations provide long-term intellectual value and impetus, methods come as attractive fringe benefits of natural product synthesis. This Account describes methodological solutions to the syntheses of natural

products—(–)-eugenial C, *Galbulimima* alkaloids GB18, GB22, GB13, and himgaline—featuring new, convergent disconnections as important problem-solving steps, which themselves were inspired by recent methods that arose from our group. Each target required the invention of first row transition metal-catalyzed cross-coupling procedures to satisfy the biological goals of the project. In these cases, synthetic strategy identified the methodological gap—the absence of stereo- and chemoselective couplings of appropriate fragments—but the tactical advantage conferred by first row metals met the challenge. These methods were competent to handle the dense, sterically encumbered motifs common to natural products, due to, in many cases, elementary steps that did not require bond formation between the hindered substrate and the metal center (i.e. inner-sphere steps), instead engaging metal ligands (i.e. outer-sphere steps). Optimized access to bioactive natural product space led to an accelerated timeline of biological characterization, fulfilling a common promise of natural products research. The integration of complex natural product synthesis, diversification and bioassay into a single PhD dissertation would have been unmanageable in a prior era. The unique ability of first row transition metals to effect Csp^3-Csp^3 cross-coupling with high chemo- and stereoselectivity has significantly lowered the barrier to reach the avowed goal of natural product synthesis and reduced the burden (real or perceived) of integrating natural products into functional campaigns.

KEY REFERENCES:

• Kotesova, S.; Gan, X.-c.; Castanedo, A.; Green, S. A.; Shenvi, R. A. Iron-catalyzed hydrobenzylation: stereoselective synthesis of (–)-eugenial C. *J. Am. Chem. Soc.* **2023**, *145*, 15714–15720. *Two sequential outer-sphere reactions—MHAT and S_H2—were proposed as the basis for stereoselective hindered fragment coupling.*

• Shevick, S. L.; Wilson, C. V.; Kotesova, S.; Kim, D.; Holland, P. L.; Shenvi, R. A. Catalytic hydrogen atom transfer to alkenes: a roadmap for metal hydrides and radicals. *Chem. Sci.* **2020**, *11*, 12401–12422. *This collaborative review outlined mechanistic considerations for MHAT, including inner- vs. outer-sphere reactions and solvent cage effects.*

• Green, S. A.; Huffman, T. R.; McCourt, R. O.; van der Puyl, V.; Shenvi, R. A. Hydroalkylation of Olefins to form Quaternary Carbons. *J. Am. Chem. Soc.* **2019**, *141*, 7709–7714. *Mn/Ni dual-catalysis allowed alkenes to be quaternized by alkyl halides and established Mn(III) β-diketonates and phenylsilane as an effective reducing system for nickel.*

1. Introduction: Cross-coupling methods that employ first row transition metals offer orthogonal reactivity to second and third row metals. Whereas the latter, precious metals, often undergo coordinative reactions via canonical, two-electron elementary steps, the former, abundant metals, can generate and engage open shell carbon intermediates via outer-sphere steps.[1] Here, the outer-sphere cross-couplings enable the formation of congested motifs in a chemoselective[2] fashion and with great chemofidelity.[3] Our group has developed a suite of hydrofunctionalizations enabled by one or two base metal catalysts that engage olefins and diverse coupling partners in unprecedented reactions (Figure 1a). These new methods have paved the way for convergent syntheses of natural products that present interesting biological questions (Figure 1b). In turn, the demands of complex syntheses have inspired the development of novel cross-coupling methods (Figure 1c), driven by the need for chemo-, regio- and stereoselectivity. This account will detail how the interplay between new method development and natural product synthesis for biological interrogation contributed to innovation in the field of first-row metal-mediated cross-coupling.

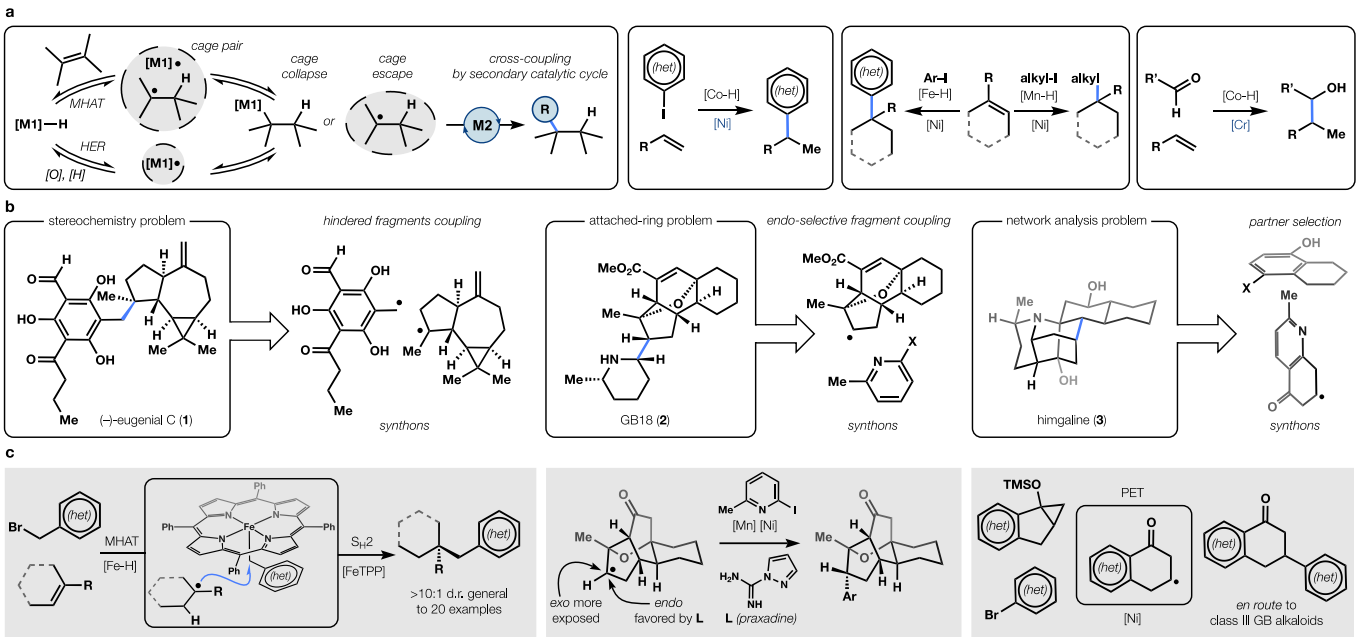

Figure 1. Overview of the Account. **a**. First-row transition metal-catalyzed cross-couplings enable general new methods involving MHAT as an outer-sphere elementary step; **b**. lessons learned from this work helped address problems in natural product chemical space: fragment coupling, stereoselectivity, strategic bond formation identified by network analysis; **c**. in turn, these disconnections led to general new methods.

2. Alkene hydrofunctionalizations by outer-sphere cross-coupling:

Formation of quaternary carbon stereocenters via Csp^3-Csp^3 cross-coupling ranks among the most challenging of reactions.[4] We thought carbon quaternization by alkene hydrofunctionalization might serve as a laudable goal due to its potential generality. After all, most quaternary carbons contain adjacent C–H bonds.[5] Furthermore, alkenes represent abundant feedstocks so their direct quaternization would circumvent substrate prefunctionalization steps. The difficulty of devising a general reaction also held appeal as we might learn new lessons in catalysis. Methods emanating from Drago-Mukaiyama hydration[6,7,8,9,10] offered a powerful entry into this area due to their robustness,[11] chemoselectivity[2] and chemofidelity.[3] These reactions have

been hypothesized to proceed via metal-hydride hydrogen atom transfer (MHAT),[12] an outer-sphere elementary step that directly generates carbon-centered radicals (open shell carbon intermediates) from alkenes.[13] MHAT tends to tolerate alkene poly-substitution, steric repulsion, and Lewis basic functional groups to a higher degree than inner-sphere, coordinative pathways characteristic of precious metals.[3,14,12] Therefore, MHAT is a particularly powerful reaction pathway for complex, natural product-like substrates, which is where our interest originated.[3,14,15,16] Many of these reactions are catalyzed by commercially available first-row transition metals complexed with inexpensive ligands (acetylacetone, acac; dipivaloylmethane, dpm; etc.), providing a barrierless entry for any practitioner.

Historically, MHAT-based methods have employed classical, stoichiometric radical traps to install heteroatomic functional groups.[17,18] In contrast, variants from our group add a secondary transition metal complex to generate catalytic concentrations of a coupling partner that engages an open-shell carbon intermediate (Figure 1a). Despite its low concentration, the high rate-constant associated with capture of the carbon radical by the secondary metal species leads to efficient overall reaction.[19,20] Nevertheless, different first-row transition metal catalysts enable complementary reactivity pathways and unique substrate tolerances based on competing elementary steps occurring at different rates. For example, MHAT dual catalysis was restricted initially to the formation of *sec*-alkyl arenes from terminal alkenes by cobalt salen-catalyzed hydroarylation, which appeared to proceed via *sec*-alkylcobalt transmetalation by an arylnickel.[21] The suitability and branched-selectivity of electron-neutral, -rich or -deficient alkenes (e.g., α-olefins, vinyl thioether, vinyl pinacol boronate) reflected the outer-sphere nature of the MHAT step, and the chemoselectivity of both cobalt and nickel catalysis allowed the use of substituted benzene electrophiles as well as heteroaromatics (Figure 2). The inherent instability of *tert*-alkyl

cobalt salen complexes prevented formation of quaternary centers under similar conditions; instead, alkene isomerization occurred via reversible MHAT.

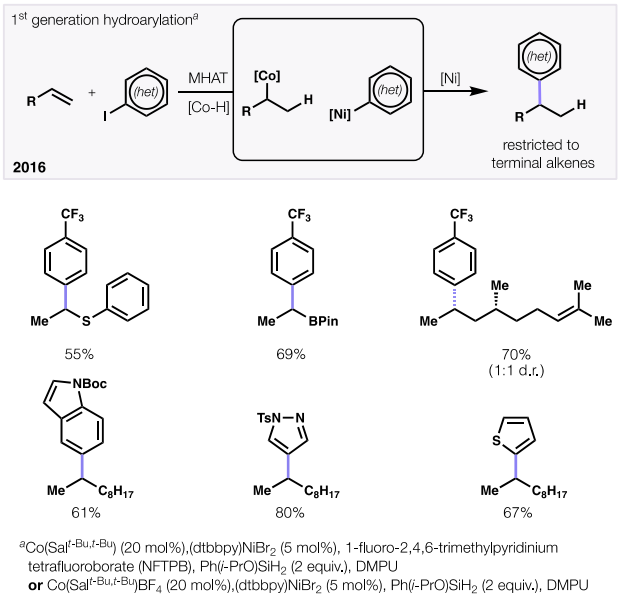

Figure 2. Initial forays into hydroarylation were restricted to terminal alkenes, reflecting the mechanism: radical collapse to a *sec*-alkyl organocobalt followed by transmetalation.

Replacement of cobalt salen with an iron β-diketonate complex expanded the hydroarylation methodology to include di-, tri- and even tetrasubstituted alkenes and form quaternary centers with broad scope.[22] We suspect that this breadth reflects the very low stability of the intermediate Fe–H complex, which appears to undergo rapid and irreversible MHAT.[23,24] Holland has even suggested that metal hydride formation, not MHAT, is turnover limiting.[25,28] As a consequence of this rapid rate of alkene engagement, *sec*-alkyl and *tert*-alkyl arenes can be formed with ease from simple, electron-neutral olefins and haloarenes. In contrast to Brønsted or Lewis acid-mediated reactions like Friedel-Crafts alkylation, a variety of acid-sensitive groups like furans, ketals, oxetanes and epoxides can be incorporated into substrates (Figure 3).

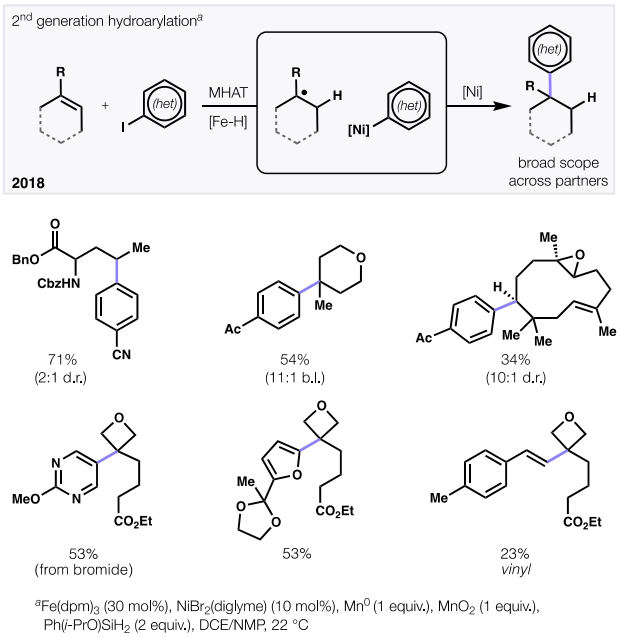

Figure 3. Rapid and irreversible MHAT from iron hydrides allow quaternary center formation.

Combination of nickel and manganese β-diketonate catalysts enabled Csp^3-Csp^3 cross-coupling,[26] likely due to the same irreversibility of Mn-catalyzed MHAT as with Fe. This reaction fulfilled a longstanding goal in the lab to realize a "carbo-Menshutkin" reaction, i.e., quaternization of a simple alkene with an alkyl halide by analogy to the quaternization of an amine (Figure 4). In this case, efficient conversion relied on the combined use of manganese and nickel. Consistent with prior work,[1,27] we suspect nickel promotes conversion of the alkyl iodide to the corresponding radical *en route* to alkylnickel formation and capture by the tertiary radical produced by MHAT. Thus, Co-, Fe- and Mn-catalyzed MHAT could be leveraged in Csp^2-Csp^3 and Csp^3-Csp^3 cross-coupling reactions that benefited from the remarkable mildness of first-row transition metal catalysis. This Mn/Ni dual-catalyzed hydroalkylation enabled the first use of an sp^3-hybridized electrophile (alkyl halide) among MHAT hydrofunctionalizations. Here, the hindered $Mn(dpm)_3$ ensured an optimal rate of MHAT to intersect the nickel/manganese catalytic cycles that engage the alkyl halide. HFIP and potassium carbonate proved to be crucial additives hypothesized to

facilitate σ-bond metathesis from phenylsilane to the Mn β-diketonate, possibly via formation of a transient alkoxysilane.[28] The reaction displayed exceptional functional group compatibility in its tolerance of esters, phthalimides, carbamates, silyl enol ethers, boronic esters, and epoxides (Figure 4). A broad range of terpenoids were successfully functionalized, enabling the transformation of simple or complex, electron-neutral alkenes. A diverse range of alkyl halides could be appended that included sensitive functional groups such as acetals, nitrogen-containing heterocycles and numerous chain lengths. The use of nickel, however, suggested some deficits: its high toxicity proscribed large scale application[29] and steric crowding of ligands about the metal suggested that more encumbered partners might resist coupling. As seen in Section 3, this second limitation was confirmed and required intersection with an alternative catalytic cycle to couple hindered partners.

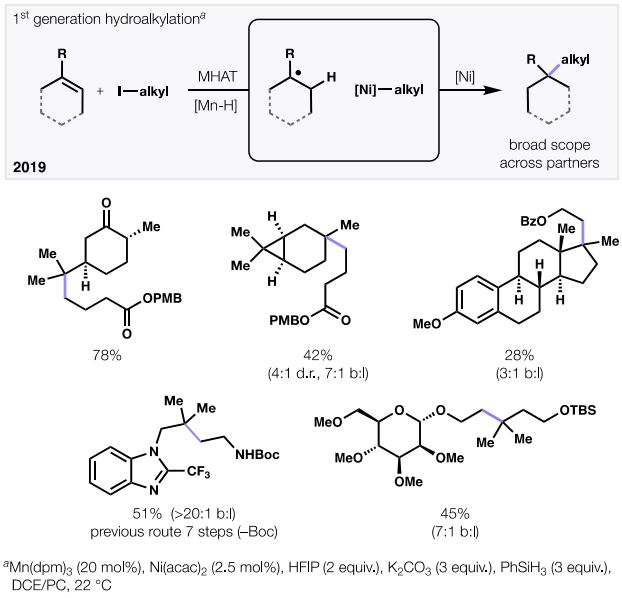

Figure 4. Hydroalkylation required a manganese hydride catalyst, which reacted with the alkene by MHAT but also served to reduce the nickel catalyst.

Finally, the combination of MHAT catalysis with chromium enabled chemistry reminiscent of carbanion reactivity to form Csp^3-Csp^3 bonds.[30] This bimetallic reaction signaled a departure from

prior work in MHAT that led alkenes to undergo traditional radical or cationic polar crossover reactivity.[31,32,33] Instead, the open-shell carbon intermediates were captured by chromium to form strong polar nucleophiles that could react with aldehydes with branched selectivity. Typically, chromium(II) serves as the active species to convert alkyl halides to alkylchromium(III) reagents for carbonyl addition,[34] which suggested that the chromium(III) salts were reduced *in situ*, either by the silane or intermediate cobalt hydride. In prior work,[19] the oxidant was implicated in rescue of the cobalt(III) catalyst, whose hydride (Co^{3+}–H) can undergo a hydrogen evolution reaction (HER) to the inactive Co(II) and must be brought back on-cycle via oxidation. The reaction scope included aromatic, heteroaromatic and aliphatic aldehydes with broad electronic variation, and tolerated reactive functional groups like esters, tosylates, and chlorides (Figure 5).

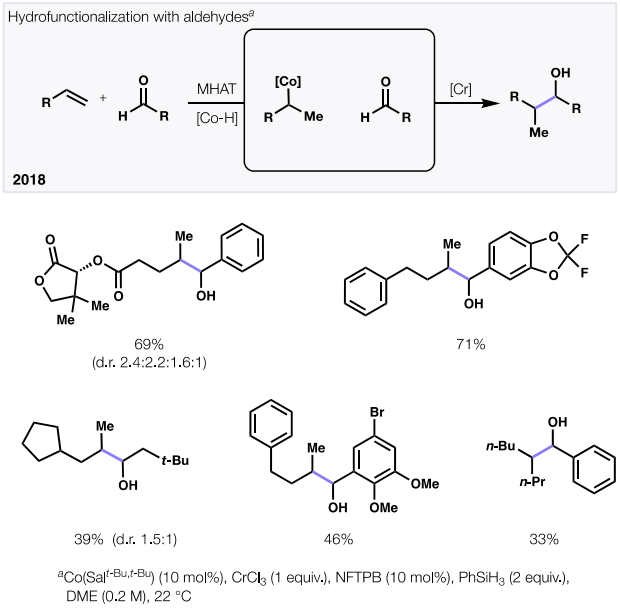

Figure 5. The mechanism of 1st generation hydroarylation inspired the use of chromium salts to transform unreactive organocobalt complexes to nucleophilic organochromium reagents.

Our foregoing research demonstrated that alkenes could undergo branch selective cross-coupling catalyzed by first-row transition metals. We hypothesized that intermediate metal hydrides might

react with the alkenes via MHAT—still a controversial proposal due to the low BDE of metal hydrides necessary[35] and the competing HER that might be expected to predominate.[36] Among the several compelling arguments that the MHAT step occurs (an outer-sphere reaction), as opposed to alkene coordination/metal insertion (an inner-sphere reaction) is the observation that increased alkene substitution does not significantly decrease reaction rate.[14] This steric tolerance lends itself to natural product synthesis, especially hindered, bi-lobed motifs common to meroterpenoids.[37] A general solution, however, requires not merely effective alkene engagement, but also efficient capture of the ensuing radical, in addition to stereocontrol in the case of many quaternary carbon stereocenters prevalent in natural products. We were curious to explore whether dual catalytic MHAT cross-coupling could solve compelling problems in complex synthesis and how the methods might be improved when subjected to a challenging substrate pair. We did not expect this exercise to lead to the development of a new cross-coupling platform competent for the diastereoselective formation of hindered Csp^3-Csp^3 bonds.

3. Eugenial C via MHAT / S_H2: two outer-sphere steps for alkene hydrofunctionalization

Our proposal for the synthesis of meroterpenoid (–)-eugenial C (**1**) was married to the development of two generations of hydroalkylation methods,[38,30] as well as the potential for these methods to interrogate the biological function of its two lobes. Biosynthetic reactions forge the unique bi-lobal structure of (–)-eugenial C convergently through Friedel-Crafts capture of a phloroglucinolmethyl cation reaction by bicyclogermacrene, followed by carbocationic rearrangement (Figure 6, top left).[39] The generality and versatility of a biomimetic route seemed low. In contrast, an MHAT cross-coupling might provide a simple and combinatorial route to **1** and its many meroterpenoid congeners (Figure 6, top right). Retrosynthetic dissection of the stereogenic quaternary center would allow us to probe the biological function of each lobe, both in the context of the

antimicrobial activity of **1** and as a general lysine adductor. An effective cross-coupling would enable these future biological goals. Perhaps the greatest challenge to surmount was skepticism from one of us (R.A.S.) that such a cross-coupling would ever be possible.

Initial forays into the synthesis of **1** were not encouraging and encountered material supply problems, low cross-coupling yields, no stereoselectivity and no catalyst turnover. As luck would have it, our chiral pool starting material, aromadendrene, suffered from pandemic-era shortages that left it backordered for months. Literature sleuthing identified a local tree, *Eucalyptus globulus*, that produced large quantities of aromadendrene and its hydrated counterpart,[40] globulol, in its woody fruits.[41] The San Diego Natural History Museum's online Plant Atlas[42] identified major groves of *E. globulus* trees just a few miles from our laboratory, allowing us to devise an effective procedure for the collection, extraction, and isolation of materials for the alkene coupling partner. Synthesis of the hexasubstituted benzyl bromide partner proved challenging due to its *o,o′*-disubstitution, which significantly reduced yields of product relative to unsubstituted partners. Late stage *o,o′*-dihydroxylations were unsuccessful. Instead, we crafted a *bis*-dioxinone substrate that tied the *ortho*- substituents into a butterfly structure to decrease steric repulsion and reduce Lewis basicity (Figure 6, middle).

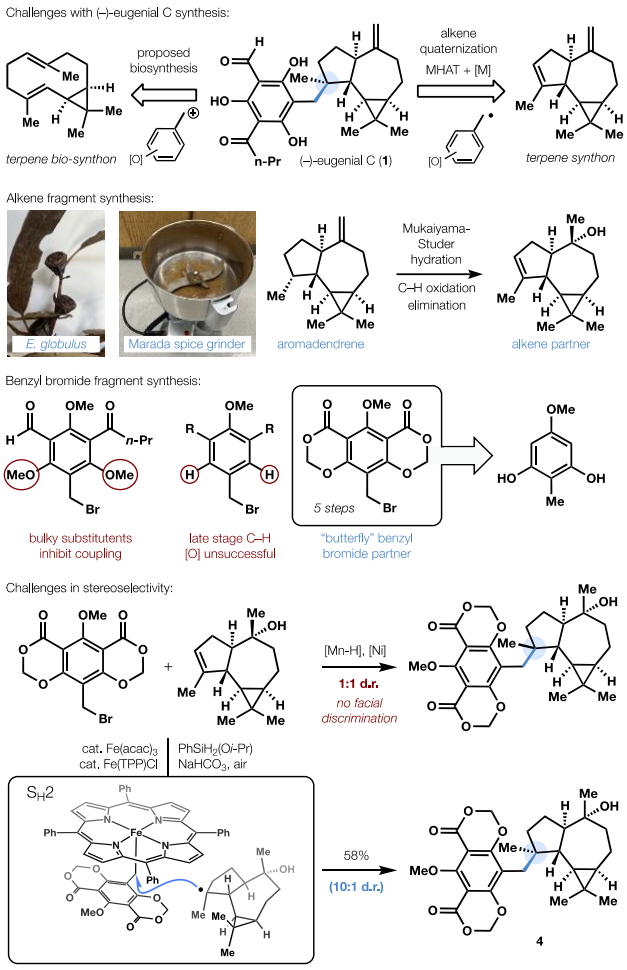

Figure 6. The strategy to synthesize antimicrobial meroterpenoid (–)-eugenial C evolved into a general method for MHAT/S_H2 coupling.

Whereas this design led to some improvements in coupling efficiencies (20–30% yield), the metal loadings stayed high (0.5–1.0 equiv.) and stereoselectivity remained stuck at 1:1 d.r. across dozens of variations including diverse ligand sets and substrate-embedded directing groups. We considered that the mechanism of C–C bond formation might be destined to fail for three different reasons: reversibly-formed diorganonickel diastereomers underwent reductive elimination at equal rates, diorganonickel diastereomers formed irreversibly at equal rates, or benzyl halides represented a special case where direct radical-radical coupling led to mixtures of diastereomers. Thus, we sought an alternative bond-forming event via an S_H2 step featured in a recent

photocatalytic Csp^3-Csp^3 cross-coupling.[43] Simple models suggested an intermediate benzyl porphyrin might encounter the distant steric environment at the radical's periphery and differentiate its prochiral faces. If successful, this approach would merge two outer-sphere elementary steps, MHAT and S_H2, to cross-couple simple building blocks and form a very hindered bond.

Despite the potential for multiple off-pathway processes—benzyl dimerization, alkene hydrogenation, radical oxidation—to contravene the productive reaction, coupling occurred effectively to deliver **4** with high diastereoselectivity (Figure 6, bottom). Iron proved more effective than manganese to promote good yields at low catalyst loading (5–10 mol%), likely due to the tendency for iron to turnover efficiently at low concentrations of O_2,[25] the lower hydridic character of Fe–H compared to Mn–H,[12,24,44] and possibly the lower rate of HER[45] associated with Fe–H. Iron became the workhorse of a new reaction system that engaged alkenes in MHAT to form a tertiary radical, and formed a benzyl iron complex that underwent S_H2. The unusual breadth of the substrate scope is captured in Figure 7.

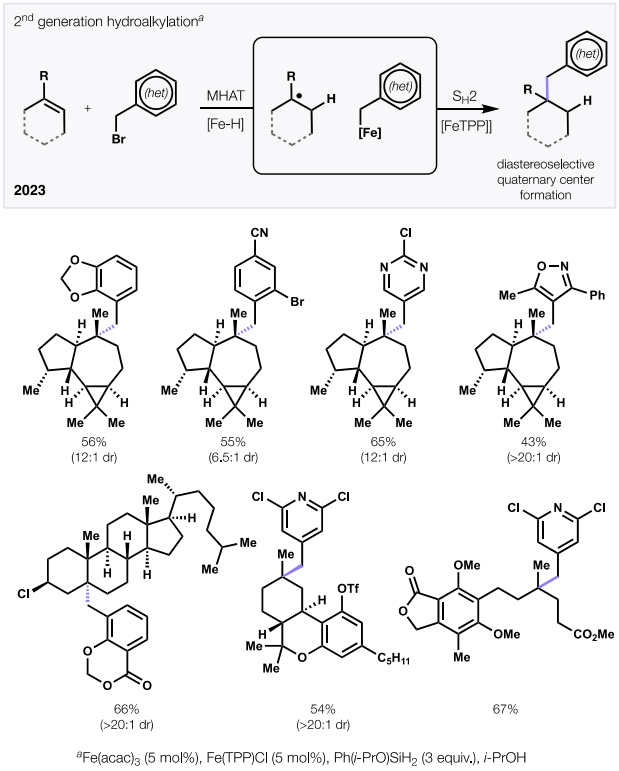

Figure 7. Iron-iron dual catalysis engages a breadth of 1,1-disubstituted and trisubstituted alkenes in two putative outer-sphere reactions: MHAT and S_H2.

The simplicity of the reaction suggests many new variants await discovery; the lower toxicity of iron compared to nickel commends this MHAT/S_H2 coupling for large scale use.[46] Developed in the context of (–)-eugenial C, most coupling partners were bound to be simpler and thus the iron-catalyzed hydrobenzylation demonstrated broad applicability to a range of heavily functionalized, natural product derived alkenes and diverse bromomethyl (hetero)arenes. The stereoselectivity of the reaction proved general and, in most cases, featured diastereomeric ratios between 10:1 to 20:1 for any given substrate (Figure 7).

The optimized cross-coupling procedure afforded quick and scalable access to (–)-eugenial C in 4 additional steps; ongoing work has produced analogs to probe function like phenotypic effects and lysine adduction. By allowing the biological questions to dictate the needs of the synthesis,

and the synthesis to drive innovation in cross-coupling, we arrived at a new direction for methodological exploration and developed an efficient platform for biological interrogation. Biological assays are currently underway to verify the antibacterial activity of eugenial C, investigate the activity of its congeners and analogs, and probe the basis for these effects.

4. GB18: ligand control over attached-ring *endo*-selectivity

Observations and mechanistic hypotheses derived from the Mn/Ni dual-catalytic hydroalkylation manifested themselves in a crucial step of another natural product synthesis, this time in the context of a cross-electrophile coupling (XEC).[47] GB18 contains a difficult tetrahedral attached-ring problem: its pendant 6-methyl-piperidine resides on the *endo*-face of a tetracyclic scaffold; both attached-ring bridgeheads are stereogenic centers (Figure 8, top). This structure caught our attention due to its potent activity in a mouse grooming assay and a literature hypothesis that it might represent the hallucinogenic principle of *Galbulimima* (GB) bark.[48,49,50,51] A cross-coupling solution to GB18 would accelerate access to large quantities of material for biological interrogation and offer an avenue for diversification to analogs to perturb pharmacology. This coupling, however, proved unusually challenging, again for reasons of chemo- and stereoselectivity. Intermediate **5** could be procured in 6 steps on multigram scale, but cross-electrophile coupling with 6-halo-picoline under a variety of standard conditions (Zn^0, Mn^0, TDAE) led to protodeiodination or ether fragmentation (Figure 8, middle). It's important to note that traditional precious metal-catalyzed arylations of **6** were unsuccessful. The iodide substituent of **5**, however, served as a homolytically-cleavable substituent on carbon that could undergo outer-sphere (relative to carbon) reactions with a reductant, analogous to the proposed, outer-sphere S_H2 reactions[52,53] available to organoporphyrins and carbon-centered radicals.[54]

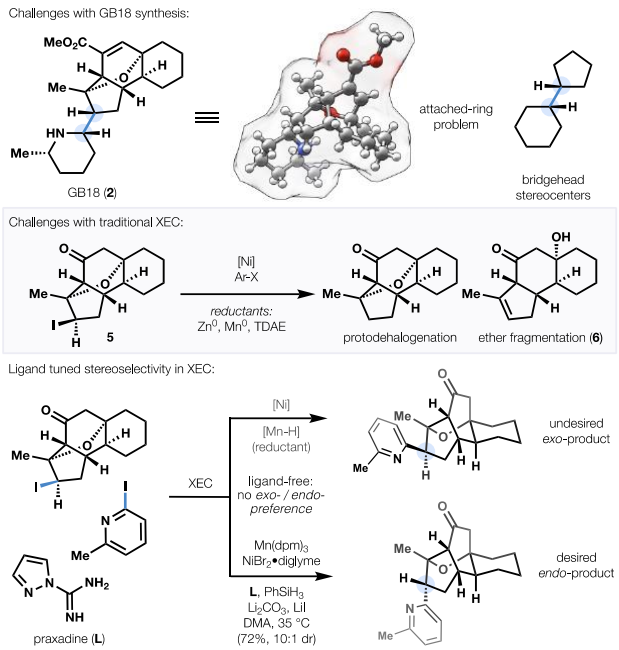

Figure 8. An attached-ring problem evolved into a need for stereo-invertive cross-coupling to append a picoline on a more hindered *endo*-face. This could be achieved with stereocontrol by an amidine ligand, which happened to be the inexpensive drug, praxadine.

Owing to the pioneering work of Weix, Reisman, and others, cross-electrophile coupling has been featured in a variety of complex syntheses, yet its application to the formation of an attached ring motif has little precedent and none for *endo*-selective coupling.[55,56] Drawing inspiration from the lab's Mn/Ni dual-catalyzed hydrofunctionalization,[26] in which the MHAT catalyst $Mn(dpm)_3$ appears necessary to reduce nickel(II) to (I), we applied the same catalytic system to the cross-electrophile coupling of **5**. Although coupled products were observed, diastereoselectivity was absent. Notably, the *endo*-isomer is destabilized by 0.5 kcal/mol relative to *exo*-, and model radical addition reactions occurred preferentially from the *exo*-face. Fortunately, a careful survey of amidine ligands, directly inspired by Weix's discovery of their privileged performance in cross-electrophile coupling,[57] unearthed a novel amidine ligand (praxadine) that favored the more

hindered *endo*-isomer by 10:1 over *exo*- (Figure 8, bottom). This ligand-controlled stereochemical inversion of iodide **5** represents an important step forward in generalized stereocontrol for organonickel/carbon radical capture independent of substrate topology. Even though this cross-electrophile coupling used the reagents of our hydroarylation, the underlying mechanism did not involve *in situ* formation of an alkene: subjection of this control substrate to the same reaction conditions yielded no product. The mechanism of stereocontrol could not be fully elucidated, however, and the complexity of the possible pathways prevented the development of catalytic conditions. We considered that the final diastereoselectivity may derive from a hydrogen-bond network between the pyridylnickel-ligand complex and the Lewis basic oxygen bridge of **5**; however, this and related models remain speculative. Elaboration of the *endo*- product to GB18 identified μ- and κ-opioid receptors as high affinity targets, whereby GB18 served as a potent antagonist ($pIC_{50} = 8$) at both targets. The ease of cross-coupling **5** with stereocontrol lends this substrate to extensive diversification by heterocycles and investigation of opioid pharmacology with this novel class. Indeed, this approach has led to >90 analogs of GB18 currently under investigation *in vitro* and *in vivo*.

5. GB22, GB13 and himgaline: siloxycyclopropane *endo*-arylation

In contrast to the stereoselective attached-ring cross-coupling featured in the synthesis of GB18, a class I alkaloid, the alternative Class III GB alkaloids presented an altogether different attached-ring problem.[58] We had aimed to use the newly isolated aromatic alkaloid GB22 as a linchpin intermediate *en route* to more complex congeners like himgaline, and traced their syntheses back through hydrogenation and Friedel-Crafts transforms to compound **9** (Figure 9, top). Similar scaffolds had been synthesized in a single step via strong acid-mediated double Friedel-Crafts reactions (Figure 9, middle).[59] These reactions failed, however, due to incompatible arene

electronics and the acid sensitivity of the product. In order to circumvent the unproductive carbocation intermediate, we targeted the corresponding carbon radical with the anticipation that nickel could mediate its capture and cross-coupling with a bromoarene partner.

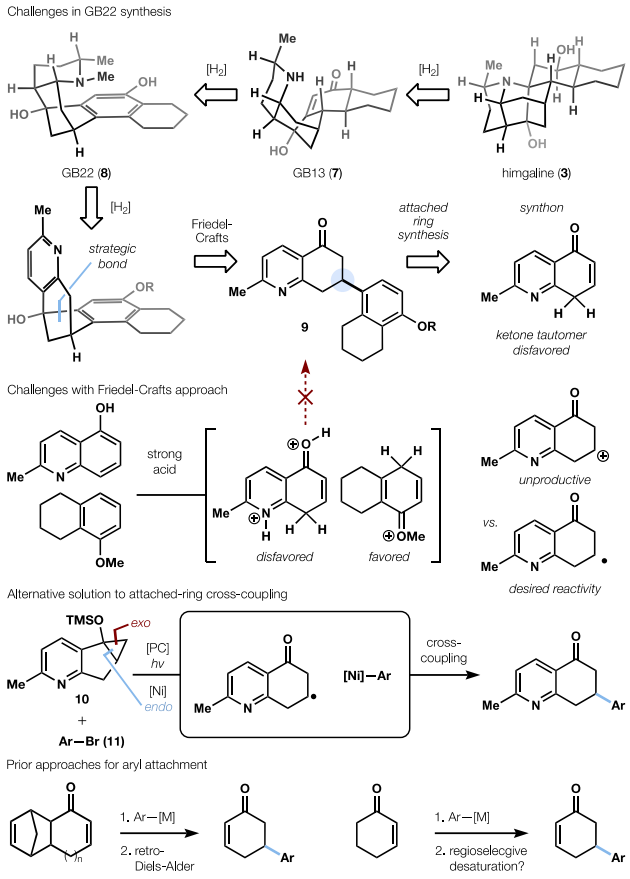

Figure 9. Himgaline could be retrosynthetically transformed to a bridging tetracycle, whose two strategic bonds could be dissected sequentially. The polar disconnection could be replaced with a new radical cross-coupling that complemented existing enone–arene attachment methods.

This convergent strategy would enable rapid access to the GB chemical space for biological exploration: in particular, the assignment of high affinity human receptors. We were inspired by Mattay's seminal work demonstrating that photoinduced electron transfer (PET) between arene dyes and siloxycyclopropanes results in the formation of β-keto radicals.[60] Capture by an

organonickel intermediate would result in net reversal of the normal regioselectivity of cyclopropanol arylations: palladium catalysts, for example, cleave the *exo*-bond on similar ring systems,[61] whereas this proposed nickel catalysis would select for the *endo*-bond (Figure 9, middle).[62,63] Indeed, subjection of pyridine siloxycyclopropane **10** and arene **11** to Zhang's carbazole-cyano-benzene PET catalyst[64] (photocatalyst, PC) in the presence of a nickel catalyst led to serviceable yields of the targeted attached-ring system. This reaction proved general across variations to both partners and provided an alternative solution for the synthesis of 5-functionalized-2,3-unsaturated cyclohexenones. Typically, this general substructure can be synthesized by protection, unsaturation, conjugate addition and deprotection, by conjugate addition, followed by selective unsaturation, or by Robinson annulation. *Endo*-selective cyclopropane ring opening offered an effective solution in the case of **9**, where none of these alternatives were productive. The nickel-catalyzed attached-ring formation served as an effective tool for route discovery, enabling the efficient advance of **9** to GB 22, GB 13, and himgaline upon strategic scouting of an optimal final sequence.

CONCLUSION

The advantages of first-row transition metals lend themselves to the most challenging problems in natural product synthesis, especially the ability to cross-couple complex, high fraction sp^3 (F_{sp3}) fragments with stereoselectivity, chemoselectivity and chemofidelity. This latter category, which describes the capacity of a reaction to occur independent of the molecular context of the reacting functional group, contrasts markedly with precious metal-catalyzed reactions of alkenes. Here inner-sphere, coordinative reactions exhibit extreme sensitivity to substitution patterns and steric repulsion from adjacent atoms, an effect minimized in MHAT reactions due to the outer-sphere nature of the reaction pathway. The new ability to combine MHAT with cross-coupling reactions

has enabled some startling results, starkly illustrated in the synthesis of (–)-eugenial C by its iron-catalyzed convergent cross-coupling of complex and hindered partners (Figures 6 and 7). Both the stereoselectivity and the efficiency of the cross-coupling likely benefit from two sequential outer-sphere reactions, MHAT and S_H2, and establish a thought-provoking paradigm for alkene functionalization. Additionally, the merger of MHAT with nickel catalysis offers solutions to related problems in fragment coupling, including tetrahedral attached-ring synthesis. These cross-coupling platforms to access (–)-eugenial C, GB18, GB22, GB13 and himgaline relate directly to goals in chemistry and biology, which continue to bear fruit as methods expand beyond the initial targets and the naturally-occurring scaffolds are diversified beyond nature's constraints.[65] The view that total syntheses are vain tales of mountain climbing—full of sound and fury, symbolizing nothing—ring hollow if sights are set beyond mere target acquisition. Instead, new cross-coupling reactions can identify profitable areas of reactivity to mine on the mountain slopes and can illuminate paths to accelerate exploration beyond the summit.

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Notes

The authors declare no competing financial interest.

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