Single catalyst double outer-sphere alkene cross-coupling

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ABSTRACT: Cross-coupling catalysts typically react and unite functionally distinct partners via sequential inner-sphere elementary steps: coordination, migratory insertion, reductive elimination, etc. Here we report a single catalyst that cross-couples styrenes and benzyl bromides via iterative outer-sphere steps: metal-ligand-carbon interactions. Each partner forms a stabilized radical intermediate yet hetero-coupled products predominate. The system is redox neutral and thus avoids exogenous oxidant, resulting in simple and scalable conditions. Numerous variations of alkene hydrobenzylation are made possible, including access to the privileged hetero-dibenzyl (1,2-diarylethane) motif and challenging quaternary carbon variants.

Alkene alkylation can occur by polar, radical and metal coordinative mechanisms, where relative rates, regioselectivities and efficiencies depend on the alkene substituent pattern.[1] Among radical methods, metal hydride hydrogen atom transfer (MHAT) cross-coupling has emerged as an effective strategy to append alkyl groups to alkenes, even to generate quaternary carbons, with consistent Markovnikov selectivity, chemoselectivity and tolerance of multiple alkene substitution patterns.[2] Prior methods have relied on radical capture of classic π-electrophiles (Fig. 1a, left)[3] or on dual catalysis to engage σ-electrophiles, whereby the MHAT catalytic cycle intersects a secondary cycle: nickel,[4] chromium,[5] copper[6] or iron[7] (Fig 1a, right).[8] We recently reported this latter cross-coupling—iron-iron dual catalysis—to enable complex fragment coupling by a putative MHAT/ S_H2 fragment mechanism (Figure 1b). As in the seminal report by MacMillan,[9,10] an S_H2 pathway was suggested by 1) a marked increase in diastereoselectivity that accompanied addition of the iron porphyrin cocatalyst, as well as 2) side products that indicated radical intermediates and 3) absence of an open valence *cis-* to the carbon ligand on iron that might otherwise indicate C–C bond formation by reductive elimination. This is similar to the reasoning that suggests iron hydrides can functionalize alkenes by an MHAT mechanism, which might itself be considered a metal hydride S_H2 reaction.

Here we identify a single iron porphyrin catalyst that appears to mediate both alkene MHAT and capture of the resulting radical in an alkyliron S_H2 (Fig 1c). This is an unusual and, to our knowledge, unprecedented type of alkene cross-coupling where a single metal catalyst mediates iterative outer-sphere bond-forming elementary steps, i.e. the catalytic metal center does not form a bond to the alkene in either bond-forming step.[11] Each alkene carbon would react with an iron catalytic intermediate where single electron density resides on a reacting ligand, as suggested previously.[12] Among the products of these cross-couplings are benzyl heterodimers,[13] privileged motifs among drug substances that are difficult to access from two benzyl fragments,[13p-u] especially to generate the quaternary carbons demonstrated here.

Our prior work required both $Fe(acac)_3$ and Fe(TPP)Cl (Fig 1c) to couple all-alkyl alkenes and benzyl bromides. The proposed intermediate, $Fe(acac)_2$–H, has been posited to undergo

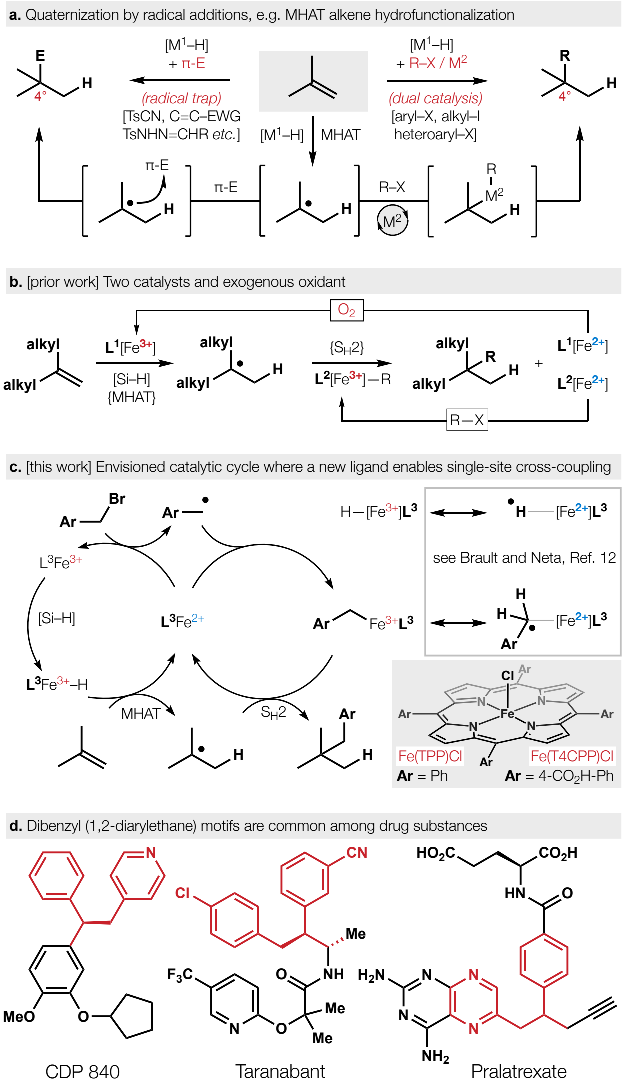
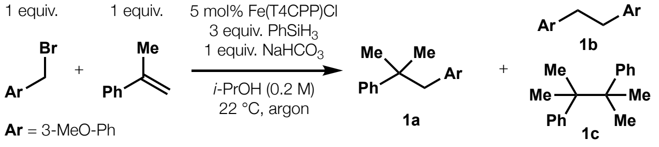


Figure 1. Prior work contrasted to current work; proposed catalytic cycles and representative substructures.

rapid MHAT with alkenes, in which its formation—not its consumption—is rate limiting and its instability drives reaction with even hindered alkenes.[14] The iron porphyrin, in turn, has been proposed to form reactive alkyliron complexes[12] subject to S_H2 by alkyl radicals.[9,10] The $Fe(acac)_3$ catalyst, however, required an air atmosphere to turn over the Fe^{2+} intermediate, a common problem in MHAT (see below).[8] We wondered if Fe(TPP)Cl itself might form an iron hydride that could undergo MHAT[15] with more reactive alkenes, but turn over by engagement of the benzyl halide coupling partner[16] (Figure 1c) instead of O_2.[17] Styrenes were chosen as test substrates because their resulting benzyl radicals might be formed by MHAT from reasonably stable Fe–H bonds.[18] This design, however, involved the intermediacy of two semi-persistent radicals that might lead to uncontrolled homo-coupling[19] and statistical mixtures (see below).

Unfortunately, Fe(TPP)Cl (entry 1) only delivered a 14% yield of heterodimer **1a** along with 6% of a styrene homodimer **1c** (12% of its theoretical maximum: a 1:1 ratio of homo- to -heterodimer). After a lengthy exploratory campaign (see SI), effective conditions were developed that 1) employed the novel iron catalyst [Fe(T4CPP)Cl] (see Fig 1c), 2) did not require oxygen and 3) delivered 87% of **1a** (5:1 ratio with **1b**), effectively outcompeting the C• dimerization pathway, despite use of a 1:1 substrate ratio. The T4CPP ligand proved unique: replacement with a sulfonic acid could not recapitulate the effect of the carboxylic acid; $Fe(acac)_3$ alone was completely ineffective (entries 4 and 5), consistent with its inability to turnover by BnBr. Addition of base ($NaHCO_3$, entry 4 and 5) proved essential, possibly a result of carbonate-silane coordination to increase Si–H hydricity,[20] quench of strong acid,[7] iron ligand exchange or ligand deprotonation. Notably, the reaction could tolerate air, but O_2 was not necessary for catalyst turnover. This stands in contrast to prior work in which O_2,[21] TBHP[22] or *N*-fluoro-collidinium[23] additives reoxidized catalysts.[8] $NaBH_4$ could replace phenylsilane (entry 7)[15,24] for large scale applications. The redox neutrality of this new single-catalyst system allows facile scaling without the constraints of mass-transfer control between the liquid phase and gas headspace. In contrast, higher material throughput of an O_2-dependent dual-iron reaction[7] required scaling-out to multiple runs at 0.1 mmols. Entry 2 scaled to 1 mmol with no change in yield (see SI).

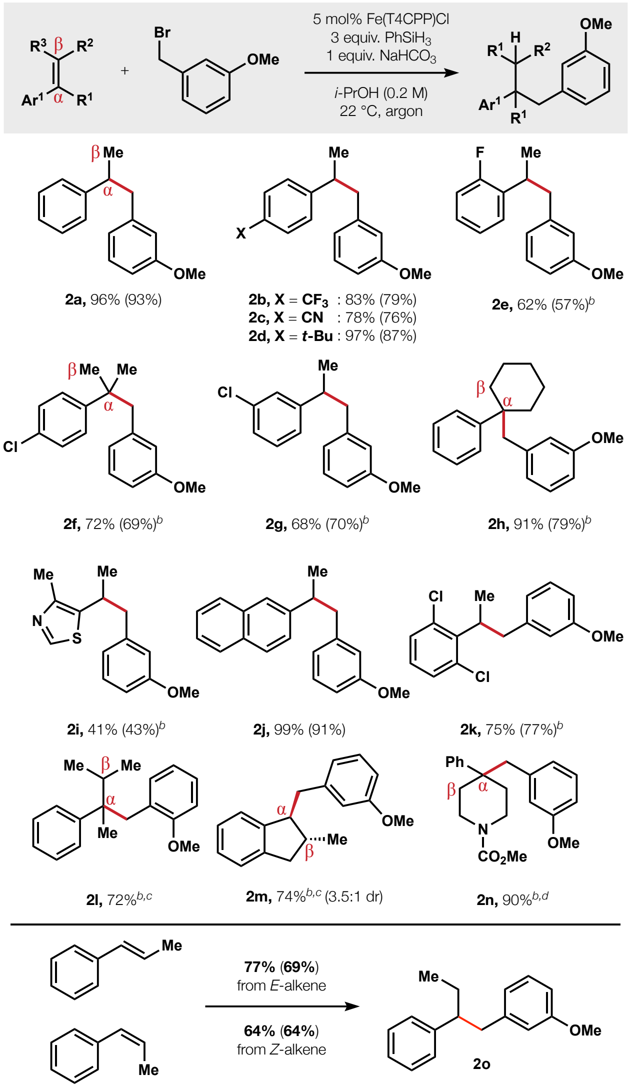
Table 1. Variations away from optimal conditions.



Entry	Variation^{a}	%**1a**^{b}	%**2**	%**3**
1	Fe(TPP)Cl not Fe(T4CPP)Cl	14	1	6
2	none	87	8	2
3	$Fe(acac)_3$	nd	nd	nd
4	Fe(T4SPP)Cl not Fe(T4CPP)Cl	10	5	2
5	no $NaHCO_3$	36	3	2
6	$CsHCO_3$ not $NaHCO_3$	45	5	2
7	$NaBH_4$ not $PhSiH_3$	65	5	9
8	2 mol% Fe(T4CPP)Cl	52	7	2

[a] T4CPP = tetra(4-carboxyphenyl)porphyrin; TPP = tetraphenylporphyrin; T4SPP = tetra(4-sulfoxyphenyl)porphyrin; [b] by ^1H NMR; theoretical yield of **1a**, **2** and **3** are 100%, 50% and 50%.

Table 2. Variation of conjugated alkene.[a]



2a, 96% (93%)

2b, X = CF$_3$: 83% (79%)
2c, X = CN : 78% (76%)
2d, X = *t*-Bu : 97% (87%)

2e, 62% (57%)^{b}

2f, 72% (69%)^{b}

2g, 68% (70%)^{b}

2h, 91% (79%)^{b}

2i, 41% (43%)^{b}

2j, 99% (91%)

2k, 75% (77%)^{b}

2l, 72%^{b,c}

2m, 74%^{b,c} (3.5:1 dr)

2n, 90%^{b,d}

77% (**69%**) from *E*-alkene

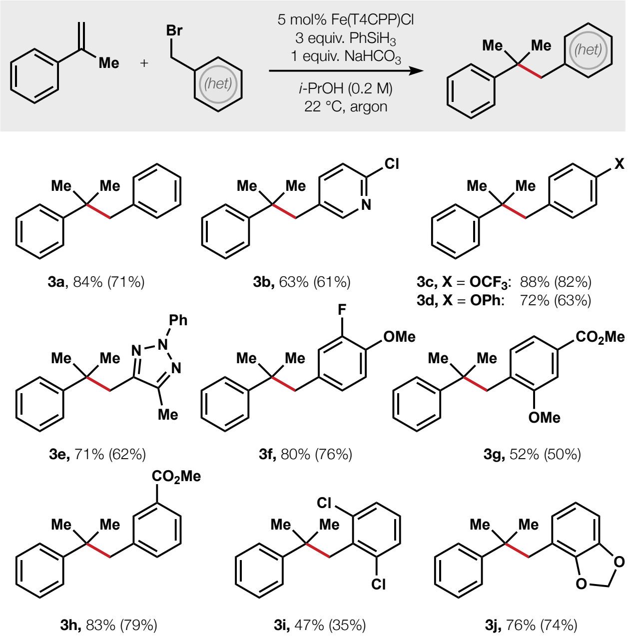
64% (**64%**) from *Z*-alkene

2o

[a] 0.2 mmol alkene and 0.2 mmol bromide, unless otherwise noted; ^1H NMR yield (isolated yield); [b] run under air, not argon; [c] 0.4 mmol alkene; [d] 0.24 mmol alkene.

The cross-coupling proved general to promote selective heterodimerization of different benzyl radicals across a wide variety of commercially available materials. To the best of our knowledge, only polymerization reactions have merged styrenes and benzyl bromides, two widespread building blocks. In these polymerization examples, benzyl radicals add to a styrene terminus (β-position), whereas in **Table 2**, the benzyl bromide connects to the internal carbon (α-position) exclusively. A variety of substituents are well tolerated in the reaction, even electron withdrawing groups that can accelerate β-addition. Cyclic styrenes performed particularly well, despite increased steric hindrance; even tetrasubstituted alkenes are productive. Hetereocycles were less effective when directly conjugated to the alkene (see SI for a list of unsuccessful partners), but a tetrahydropyridine (precursor to **2n**) was among the best performing substrates.

Table 3. Variation of arylmethyl bromide[a]



3a, 84% (71%)

3b, 63% (61%)

3c, X = OCF$_3$: 88% (82%)

3d, X = OPh: 72% (63%)

3e, 71% (62%)

3f, 80% (76%)

3g, 52% (50%)

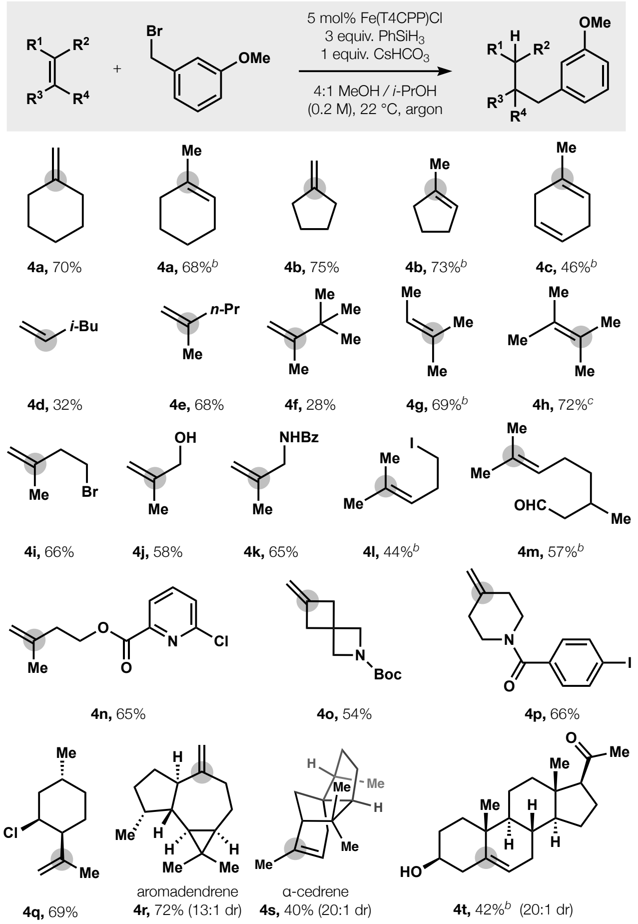
3h, 83% (79%)

3i, 47% (35%)

3j, 76% (74%)

[a] 0.2 mmol alkene and 0.2 mmol bromide

Table 4. Unconjugated alkenes and natural product scaffolds.[a]



4a, 70%

4a, 68%[b]

4b, 75%

4b, 73%[b]

4c, 46%[b]

4d, 32%

4e, 68%

4f, 28%

4g, 69%[b]

4h, 72%[c]

4i, 66%

4j, 58%

4k, 65%

4l, 44%[b]

4m, 57%[b]

4n, 65%

4o, 54%

4p, 66%

4q, 69%

4r, 72% (13:1 dr)

4s, 40% (20:1 dr)

4t, 42%[b] (20:1 dr)

[a] 0.4 mmol alkene and 0.2 mmol bromide, unless otherwise noted; [b] 0.5 mmol alkene [c] 0.6 mmol alkene

Ortho- substitution did not have a major impact on yield, even from 2,6-dichloro-α-methylstyrene, where di-planarity of the arene-alkene π-system is obstructed severely, suggesting that conjugation is not required for efficient MHAT. Similarly, *Z*- and *E*-β-styrenes reacted with comparable efficiency, even though the *cis*-alkene is rotated out of conjugation (see also **Table 4**).

The benzyl bromide scope (**Table 3**) showed broad efficiency for coupling with α-methylstyrene to form quaternary carbons, even with *ortho*-substitution adjacent to the bromomethyl coupling site. As in the styrene scope, electron-rich and -deficient partners worked well. Heterocycles, however, were restricted to low Lewis basicity/ low nucleophilicity motifs to prevent self-alkylation and coordinative deactivation of the iron catalyst.[25] It is noteworthy that common methods to access 1,2-diarylethanes[13] do not lead to quaternary carbons, and the less-common Kumada[26a] or Negishi[26b] approaches rely on stoichiometric, *neo*-pentyl organometallics. In contrast, the quaternary carbons produced in **Table 3**, can be formed under mild conditions and in protic solvent.

As suggested by the efficiency of *o,o′*-disubstituted styrenes and *(Z)*-β-methyl-styrene, conjugation did not appear necessary for iterative MHAT and coupling. Indeed, only minor changes to conditions ($CsHCO_3$ and MeOH cosolvent, see Table 4 and SI) allowed electron-neutral alkenes to be engaged by the single catalyst system. As is common in MHAT reactions,[8] 1,1-disubstituted alkenes performed better than all substitution patterns, whereas monosubstituted alkenes performed the worst. Nevertheless, aryl- and even alkyl iodides were tolerated, as were amides, esters, ketones and even aldehydes, highlighting the chemoselectivity of the cross-coupling. Additionally, the outer-sphere nature of both alkene functionalization steps allowed hindered alkenes to be engaged with reasonable efficiency: a rare feat in cross-coupling methodology.

To avoid confirmation bias, we entertained alterative mechanistic scenarios to explain C–C bond formation in the cross-coupling: 1) direct C• C• heterodimerization with suppression of one C• concentration by persistent Fe(II);[27] 2) polar (S_N2) C–C bond formation;[13q-s] 3) coordination / migratory insertion; 3) radical (S_H2) bond formation.[9] The sum of the data, however, points to S_H2 between a substituted benzyl radical and a primary alkyl iron.

For example, β-pinene as substrate leads to a 3:2 mixture of unrearranged and rearranged (U:R) hydrobenylated products (Figure 5a), indicative of radical ring opening. The corresponding anionic or organometallic pathways to ring opening are unlikely: protic solvent would immediately quench a *tert*-alkyl carbanion and steric repulsion from *gem*-dimethyls would preclude iron porphyrin approach *syn* to the cleaving cyclobutane bond. Furthermore, benzyl dimerization occurs in high yield when alkene is excluded (Figure 5b), consistent with Fe(II) reduction of the benzyl bromide and ruling out XAT as a C–Br homolysis pathway. The intermediacy of benzyl bromide-derived radicals are also signaled by clear benzaldehyde byproduct peaks in the ^{1}H NMR. We considered that the styrene-derived radical may be generated reversibly to suppress styrene homodimers, but according to deuterium labeling MHAT occurs irreversibly (Figure 5c) suggesting that S_H2 outcompetes radical-radical dimerization. Similarly, we thought selective heterodimerization might occur by C• C• collision if the concentration of benzyl bromide-derived radical were suppressed[27] by iron and a hindered styrene-derived radical were incapable of dimerization.[28] However, the diastereoselectivity of an unambiguous radical-radical dimerization[29] (1.5 : 1 dr) (Figure 5d) differed significantly from the iron-catalyzed hydrobenzylation (4 : 1 dr), suggesting that the C–C bonds form by different mechanisms.[9,30] Furthermore, direct radical-radical coupling required excess primary benzyl partner to achieve appreciable heterocoupling, which occurred in low yield and low selectivity. Preference for a heterodimer using iron catalysis likely reflects the different stabilities of 1°, 2° and 3° C–Fe complexes[10]: equilibria would disfavor *tert*-alkyl iron porphyrin complexes, which homolyze above 0 °C.[31,32] Taken together, polar and alkene coordination pathways, as well as C• C• bond formation, appear unlikely mechanisms, whereas MHAT / S_H2 governed by the single Fe(T4CPP)Cl catalyst fits the data well and enables high preferences for heteroselectivity.

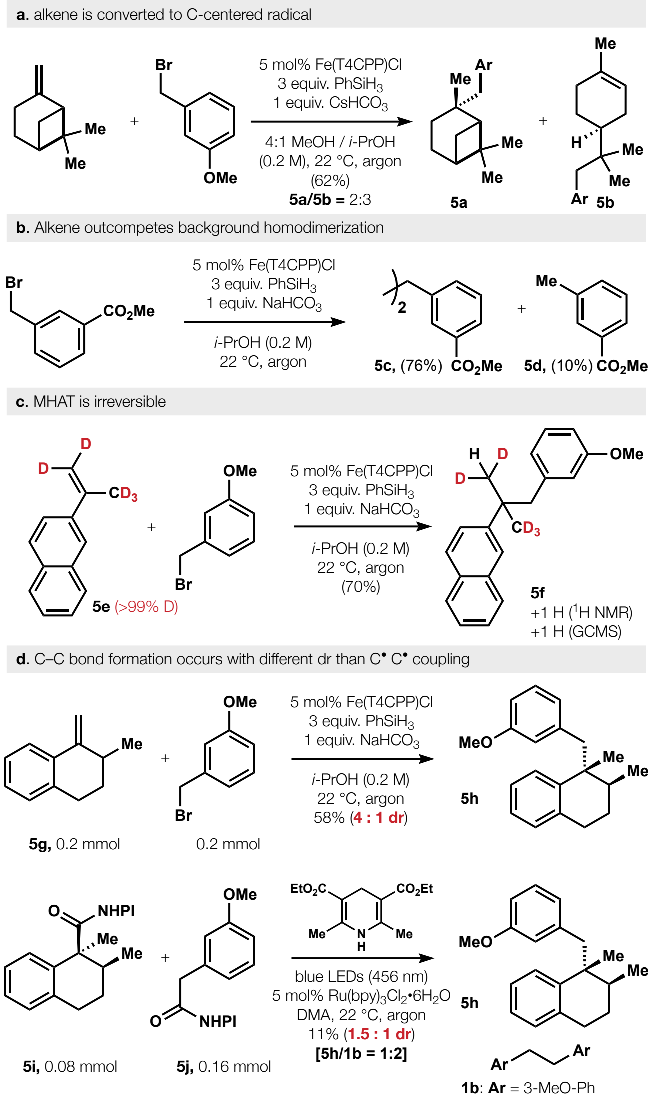


Figure 2. Experiments relevant to mechanism of C–C bond formation.

Conclusion. We have identified an iron porphyrin catalyst [Fe(T4CPP)Cl] that is effective to cross-couple alkenes with benzyl bromides via radical intermediates, even when two benzyl radicals of similar stability are formed as intermediates. This "radical sorting" strategy[10] has proven effective in dual catalysis systems with intersecting cycles; disclosed here is compression of reactivity into a single catalyst. In addition, no prior method has coupled two different benzylic radicals, which can undergo competitive background homodimerization. The basis for the unique behavior of Fe(T4CPP)Cl versus Fe(TPP)Cl is unclear but may relate to its aggregation state and/or its partition between different elementary steps in the catalytic cycles. This investigation is underway. Fe(T4CPP)–H must also cause an alkene MHAT faster than a hydrogen evolution reaction (HER) between two iron hydrides,[8] possibly by polarization of the intermediate Fe–H bond to provide it protic character. We cannot conclusively rule out HAT from a ligand-bound hydrogen,[33] although isotope labeling of related ligand classes has not uncovered evidence of metal to carbon migration of hydride.[8,34] Because the alkene reduces the Fe^{3+}–H to Fe^{2+} and the benzyl bromide oxidizes Fe^{2+} to Fe^{3+}, the catalytic cycle is redox neutral overall and thus circumvents the need for exogenous oxidant. The coupling scope includes mono-, di-, tri- and tetrasubstituted alkenes among conjugated and unconjugated alkenes alike. When styrenes are used as substrates, two similar benzyl radicals are produced as intermediates, yet the heterodimeric products predominate. The hypothesis that best fits the data involves sequential MHAT and S_H2 steps (see Figure 1) mediated by the same iron porphyrin catalyst.[15] In contrast to precious metal catalysts, alkenes are functionalized by these base metal complexes without the need for either carbon to coordinate the metal center. As a result, these systems represent powerful platforms for the synthesis and modification of natural products in which alkenes are often crowded and unreactive towards traditional metal complexes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Materials and methods, experimental procedures, copies of NMR spectra (PDF).

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TOC Graphic: