Iron-catalyzed hydrobenzylation: stereoselective synthesis of (–)-eugenial C

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Metal-hydride hydrogen atom transfer (MHAT) has emerged as a useful tool to form quaternary carbons from alkenes via hydrofunctionalization. Methods to date that cross-couple alkenes with sp^3 partners rely on heterobimetallic catalysis to merge the two cycles. Here we report a monometallic cross-coupling via putative MHAT/S_H2 steps that solves a key stereochemical problem in the synthesis of meroterpenoid eugenial C and obviates the need for nickel in these hydrobenzylations generally. The concise synthesis benefits from a conformationally-locked *o,o'*-disubstituted benzyl bromide and a locally-sourced chiral pool terpene coupling partner.

Eugenial C (**1**, Figure 1a), a meroterpenoid isolated from the fruit of *Eugenia umbelliflora*, was reported to exhibit selective antibacterial activity against *S. aureus,* including MRSA strains (resistant to β-lactams), at minimal inhibitory concentrations lower than 1 μg/mL,[1] comparable to vancomycin, daptomycin and bithionol.[1, 2] Its challenging structure consists of two lobes—a non-symmetric hexasubstituted benzene and an aromadendrene—merged at a quaternary carbon stereocenter. We were curious to understand the role of both moieties in bactericidal activity and whether they acted independently or in concert — a question best answered by modular synthesis. Eugenial C and its congeners are thought to arise[1] via *o*-quinone methide-initiated cyclization of a bicyclogermacrene followed by E1 elimination.[3] This cationic approach significantly reduces complexity but at the cost of modularity. An alternative carbon radical disconnection, we thought, would allow for selective cross-coupling of simple building blocks in a way that would lend itself to focused library synthesis and biological interrogation.[4]

We previously reported a method for the synthesis of quaternary carbons via alkene hydroalkylation by alkylhalides.[5] This transformation occurred via Mn/Ni dual catalysis: the Mn catalyst reacted with an alkene via a proposed MHAT step[6] and the Ni catalyst reacted with the alkylhalide to forge a C–C bond after C• capture and reductive elimination[7] of a putative dialkylnickel[8] (Figure 1b, left). Direct application to the synthesis of eugenial C, however, failed due to: (1) the steric encumbrance of the 2,6-disubstituted benzyl halide coupling partner and (2) the inability of ligands on nickel to favor the 4'*(R)*-stereoisomer of the natural product (**1**). Here we report a solution to both problems using monometallic catalysis: engagement of both alkene and benzyl halide by iron.[9] The predominant pathway to stereoselective C–C bond formation appears to involve sequential MHAT[10,6,11] and S_H2 steps.[12–16]

Development of an effective cross-coupling method required access to appropriate coupling partners on large scale so that optimization of multiple parameters could be carried out. The phloroglucinol portion, while superficially trivial, could be introduced in numerous forms—fully functional or protected, symmetric or non-symmetric, hexasubstituted or partly substituted (see Scheme 2 below)—each of which required independent synthesis. Identification of a successful strategy involved extensive trial and error. Access to the aromadendrane moiety (**2**) benefited from local sourcing: closely related terpenoids aromadenrene and globulol occur in abundance in the fruits of *Eucalyptus globulus* (Figure 1b, right),[17] which grow throughout the San Diego region where we live.

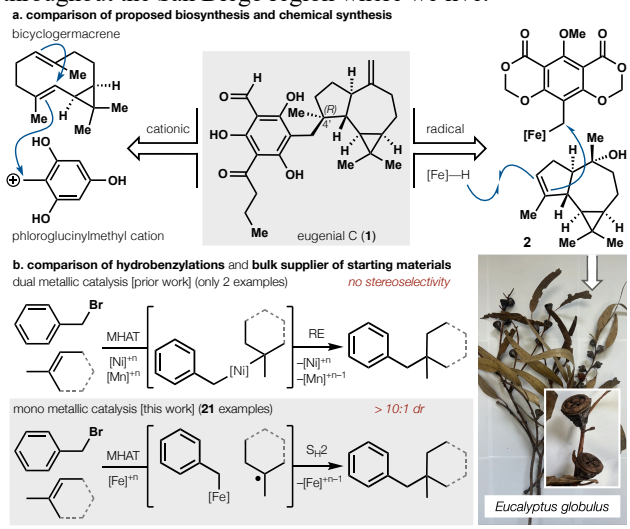
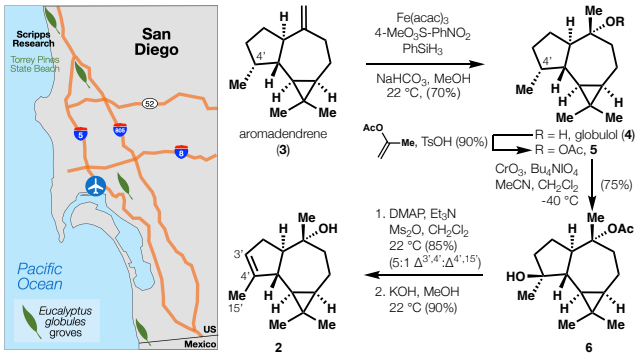


Figure 1. Overview. **a.** Proposed biosynthesis versus proposed chemical synthesis; **b.** Prior coupling via reductive elimination versus proposed coupling via S_H2 (left), and convenient source of starting materials (right).

Aromadendrene (**3**, Scheme 1) was noted as an optimal starting material due to its commercial availability, but pandemic-era shortages and the absence of **3** in commercial samples of Eucalyptus leaf oils prevented access.[18] We identified *Eucalyptus globulus* as a high-abundance producer species[17] and found its regions of abundant growth using the publicly available Plant Atlas Project administered by the San Diego Natural History Museum. [19] Fortunately, this species abounds in our local region due to 19th century planting efforts to establish *Eucalyptus* species as arid-region economy crops.[20] *E. globulus* fruits litter the ground among stands of *ca.* 20 trees located about 2 km from our laboratory. Fallen fruits were ground to a fibrous mass using a Marada 2 kg stainless-steel high power electric

spice grinder (see SI), extracted with Et_2O and concentrated *in vacuo* to a crude oil that contained 10.6% aromadenrene (**3**, average of 10 extractions), in addition to 2.2% 10'-*epi*-globulol (eugenial C numbering) and 4.8% globulol (**4**). In a typical isolation, 3.2 kg of fallen *E. globulus* fruits were gathered in 1 h; extraction yielded 284 g of a light oil that could be separated into 13.2 g globulol and 29.3 g aromadendrene. Studer's diastereoselective Mukaiyama hydration[21] of **3** to **4**, followed by acetylation converged the separate *E. globulus* fruit extract constituents into a single material **5** for large-scale processing.[22]

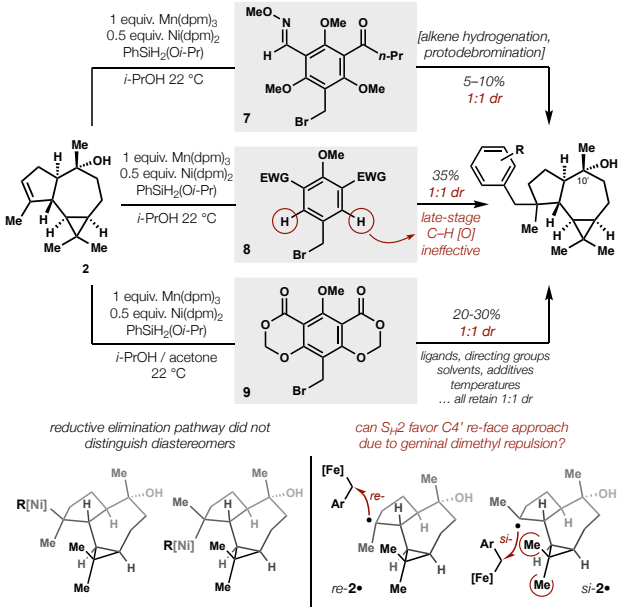


Scheme 1. Plant Atlas (Ref. 19) provided leads for sourcing aromadendrene (**3**) and globulol (**4**), which can both be advanced to coupling partner **2** via selective C–H hydroxylation and elimination.

Aromadendrene (**3**) had been reported to undergo regio- and stereoselective C–H oxidation at C4' using ozone, but concomitantly with alkene cleavage.[21a] A similar oxidation of **5** could be accomplished with dimethyldioxirane (DMDO), methyl(trifluoromethyl) dioxirane (TFDO), or RuO_4 (generated *in situ*), but reproducibly high yields of **6** were observed only with CrO_3 /*n*-Bu_4NIO_4 via a putative Cr(VI) peroxide.[23] Methanesulfonic anhydride mediated an *endo*-selective alcohol elimination of **6** (5:1 $\Delta^{3',4'}$: $\Delta^{4',15'}$). Deacetylation by potassium hydroxide delivered **2** in good yield on multigram scale.

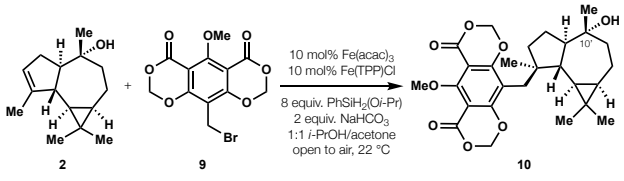
Identification of an effective hydrobenzylation coupling partner required extensive work at the strategic and methodological level to optimize steric and electronic features that led to high yields while also searching for substrate/catalyst combinations that led to high diastereoselectivity (Scheme 2a). First, we explored a fully functional, non-symmetric benzyl bromide (**7**) that contained all functionalities or equivalent groups. *O,o'*-disubstitution of the arene, however, led to low yields and never favored the desired diastereomer. Second, we removed the offending *ortho*-substituents to probe cross-coupling and late-stage C-H hydroxylation. Hydrobenzylation of **8** occurred in modest yield using variations on our reported protocol.[5] However, *o,o'*-dihydroxylation of the products failed with nine separate procedures[24] using nitrile, amide, carboxylic acid and oxime directing groups, largely stalling at mono-functionalization under dozens of variations to the published protocols. Third and finally, we reasoned that *o,o'*-disubstitution might be tolerated if the groups were restrained into an acetal that 1) limited steric clash with benzylmetal complexes and 2) delocalized Lewis basic *ortho*-oxygen non-bonding orbitals into the σ^*_{C-O} of the ester oxygen to limit chelation. This strategy was modestly successful: the symmetric *bis*-dioxinone **9** engaged alkene **2** in hydrobenzylation using Mn/Ni dual catalysis—the first example of a *o,o'*-substituted partner in hydrobenzylation. Our excitement was short-lived. Diastereoselectivity proved consistently poor across hundreds of variations to substrate, ligand, solvent, additives and temperatures.

As we struggled with stereocontrol, a study of a novel iron porphyrin-catalyzed decarboxylative cross-coupling of NHPI esters and alkyl bromides reported an increase in diastereoselectivity (1:1.1 dr to 3.2:1 dr) in the presence of an iron porphyrin as one piece of evidence consistent with C–C bond formation via alkyl-Fe(III) S_H2.[12] Similarly, if dialkylnickel diastereomers (Scheme 2b)[25] or radical heterodimerization led to low dr, differentiation of globulyl radical (**2•**) *re*- and *si*-faces might better occur by irreversible S_H2 of an alkyl-iron porphyrin, where steric repulsion from the geminal dimethyl cyclopropane would obstruct *pseudo*-equatorial approach. Independent of this question of diastereoselectivity, it was unclear whether benzyl radicals could engage iron porphyrins productively versus dimerize competitively, or whether an S_H2 elementary step could effectively outcompete common pathways in MHAT catalytic cycles like hydrogenation and isomerization.[36]



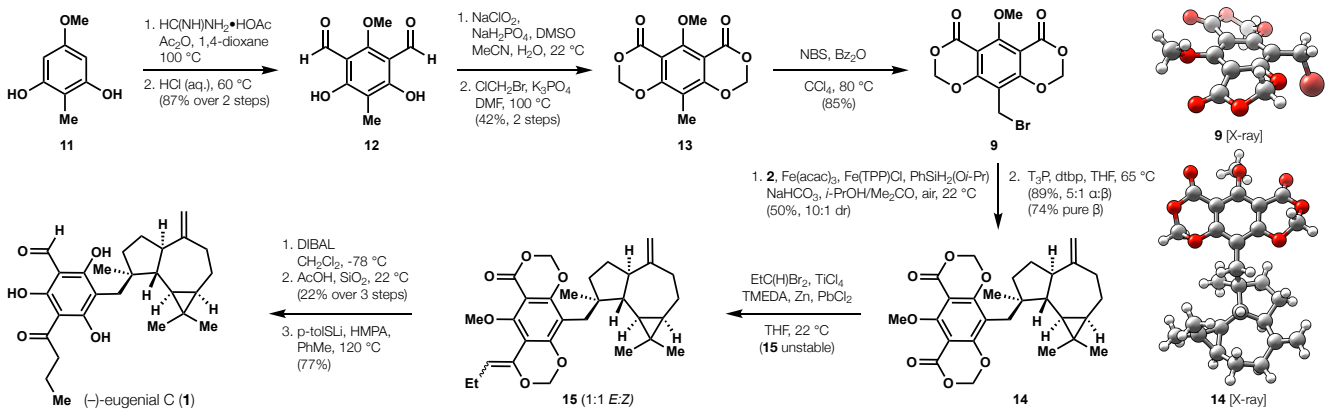
Scheme 2. Examples of failed strategies. **a.** *o,o'*-disubstitution inhibits coupling, **b.** late-stage double C–H oxidation fails, but **c.** conformational restriction leads to moderate yields. No strategy led to diastereoselectivity, leading to a hypothesis for S_H2-mediated coupling inspired by Ref. 12.

Table 1 displays the optimal conditions after extensive screening (entry 1; see Figure 2 for a proposed catalytic cycle) and deviations from these conditions. To our relief, capture of the proposed globulyl radical (**2•**) resulted in high selectivity to



Entry	Deviations from above[a,b]	yield	dr
1	none	50%	> 10:1
2	$Fe(dpm)_3$ instead of $Fe(acac)_3$	39%	> 10:1
3	$Mn(dpm)_3$ instead of $Fe(acac)_3$	trace	–
4	1 equiv. $Mn(dpm)_3$, no FeL_n	5%	1 : 1
5	$PhSiH_3$ and $NaHCO_3$	<10%	–
6	$PhSiH_3$ and K_2CO_3	35%	> 10:1
7	no $Fe(acac)_3$	none	–
8	no Fe(TPP)Cl	<5%	–
9	no $NaHCO_3$	20%[c]	> 10:1
10	no air	<10%	–

Table 1. [a]0.1 mmol **2**, 0.05 mmol **9**; [b]TPP = tetraphenylporphyrin, [c]28% dehydration of the C10' alcohol



Scheme 3. 11-step synthesis of (–)-eugenial C via MHAT-S_H2 hydrobenzylation. NBS = *N*-bromosuccinimide; DMF = *N*,*N*-dimethylformamide; acac = acetylacetonate; TPP = tetraphenylporphyrin; T3P = propylphosphonic anhydride; dtbp = 2,6-di-*tert*-butylpyridine; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; DIBAL = di-*iso*-butylaluminium hydride; HMPA = hexamethylphosphoramide.

favor the desired C4' *(R)* diastereomer (for NOE and X-ray data, see SI). Whereas we had investigated $Fe(dpm)_3$ originally due to the proposed ability of bulky dpm (dipivaloylmethane) ligands to limit off-cycle hydrogen evolution,[28,37] the less expensive $Fe(acac)_3$ was more effective in this case (entry 2), likely due to clash of the hindered substrate alkene **2** with dpm metal hydride complexes. $Mn(dpm)_3$ proved too efficient a hydrogenation catalyst and limited cross-coupling yields (entry 3). However, we did observe small amounts of product using $Mn(dpm)_3$, likely arising from direct radical-radical heterodimerization but delivering 1:1 dr (entry 4). Mono-*iso*-propoxyphenyl silane ($PhSiH_2O$*i*-Pr, RubenSilane) resulted in significantly higher yields than phenylsilane (entries 5 and 6), consistent with prior studies that demonstrated its higher rate of metal hydride formation.[26,11d] Both $Fe(acac)_3$ and Fe(TPP)Cl (TPP = tetraphenylporphyrin) catalysts were necessary (entries 7 and 8), although ongoing work in our lab suggests that the iron porphyrins can mediate the MHAT step in other contexts.[27] Weak base was essential for substrate **9** (entry 9), whose C10' tertiary alcohol can undergo acid-catalyzed elimination. As in prior reports, an atmosphere of air was employed, likely to turn over the HAT catalytic cycles and/or rescue off-cycle reduced catalysts.[28]

This diastereoselective MHAT / S_H2 cross-coupling proved crucial to the development of a streamlined, 11-step synthesis of (–)-eugenial C (Scheme 3). Conformationally-restricted benzyl bromide **9** was synthesized from dimethyl phloroglucinol **11** (listed commercially or accessible from 2,4,6-trihydroxy-benzaldehyde) by a short sequence of double formylation, double oxidation and quadruple alkylation. Bisphenol **11** was formylated by heating with formamidine acetate followed by acidic hydrolysis to **12**. Facile Pinnick oxidation allowed us to explore cyclization strategies. Formation of the intermediate *bis*-dioxinone in this latter step required extensive optimization due to the build-up of strain resulting from electron repulsion between non-bonding orbitals on the three oxygen atoms that line the northern border (see X-ray of **9** for dihedral angles). The use of $ClCH_2Br$ was ultimately successful, while alternative procedures[29] that relied on CH_2Br_2, FCH_2I,[30] formaldehyde,[31] or trioxane and catalytic Brønsted or Lewis acids[32] all failed. Radical C–H bromination occurred smoothly to deliver **9** on gram-scale. The optimized cross-coupling reaction with globulol-derivative **2** proceeded as reported above, and was followed by phosphonic anhydride-mediated elimination of the C10' tertiary alcohol[33] that delivered a crystalline material to support prior NOE-based assignments of relative stereochemistry; X-ray crystallography also assigned the absolute configurations conclusively (Flack parameter = 0.01(7)). Selective derivatization of the symmetrical *bis*-dioxinone to the *n*-propyl ketone / benzaldehyde motif was carried out by a variant of Takai olefination using catalytic $PbCl_2$,[34] which resulted in selective mono-olefination and an inconsequential 1:1 mixture of *E*/*Z* stereoisomers. This olefination served to install the 3 carbons of the *n*-propyl ketone of **1** while also allowing for selective mono-reduction of the remaining dioxinone with DIBAL; work-up with acetic acid/SiO_2 hydrolyzed the enol ether ketal to its *n*-propyl ketone. Unsuccessful attempts to achieve the same selective functionalizations included conversion of **14** to the *bis*-(*N*-alkoxy) (Weinreb) amide, which only yielded either the *bis*-aldehyde or tertiary alcohol upon nucleophile addition. Alternative olefinations using Peterson or Takeda conditions were similarly unsuccessful. Finally, *O*-demethylation by lithium *p*-thiocresolate completed the synthesis of (–)-eugenial C, whose spectroscopic properties (^1H, ^{13}C NMR, HRMS) proved identical in all respects to those from its isolation.[35] The optical rotation of synthetic **1** ($[\alpha]_D$ –4, c 0.05, $CHCl_3$) differed slightly from that of isolated **1** ($[\alpha]_D$ –7, c 0.13, $CHCl_3$), perhaps a result of the error associated with low specific rotation.

The iron-catalyzed cross-coupling optimized for **2** and **9** could be applied to a broad range of substrates and provided general access to hindered, methylene-bridged products (Table 2). The remarkable alignment of catalytic cycles helped suppress side-products commonly associated with our first-generation conditions, such as alkene hydrogenation, isomerization and hydration, as well as benzyl bromide proto-dehalogenation and oxidation to a benzaldehyde. Due to the large-scale availability of aromadendrene via isolation from *E. globulus*, we first explored the breadth of benzyl bromide tolerance with this complex 1,1-disubstituted alkene. Very little difference in reaction efficiency was observed between electron-poor and electron-rich arenes; the only effect of ortho substitution was to vary diastereoselectivity, which in most cases exceeded 10:1 dr. We also investigated several heterocyclic benzyl bromides, which have wide commercial availability (~2000) and are simple to access by radical bromination. The few that we tested all coupled with high stereoselectivity, although reductively labile rings like isoxazoles led to modest yields (39–43%). The breadth of the alkene scope surprised us, especially given the

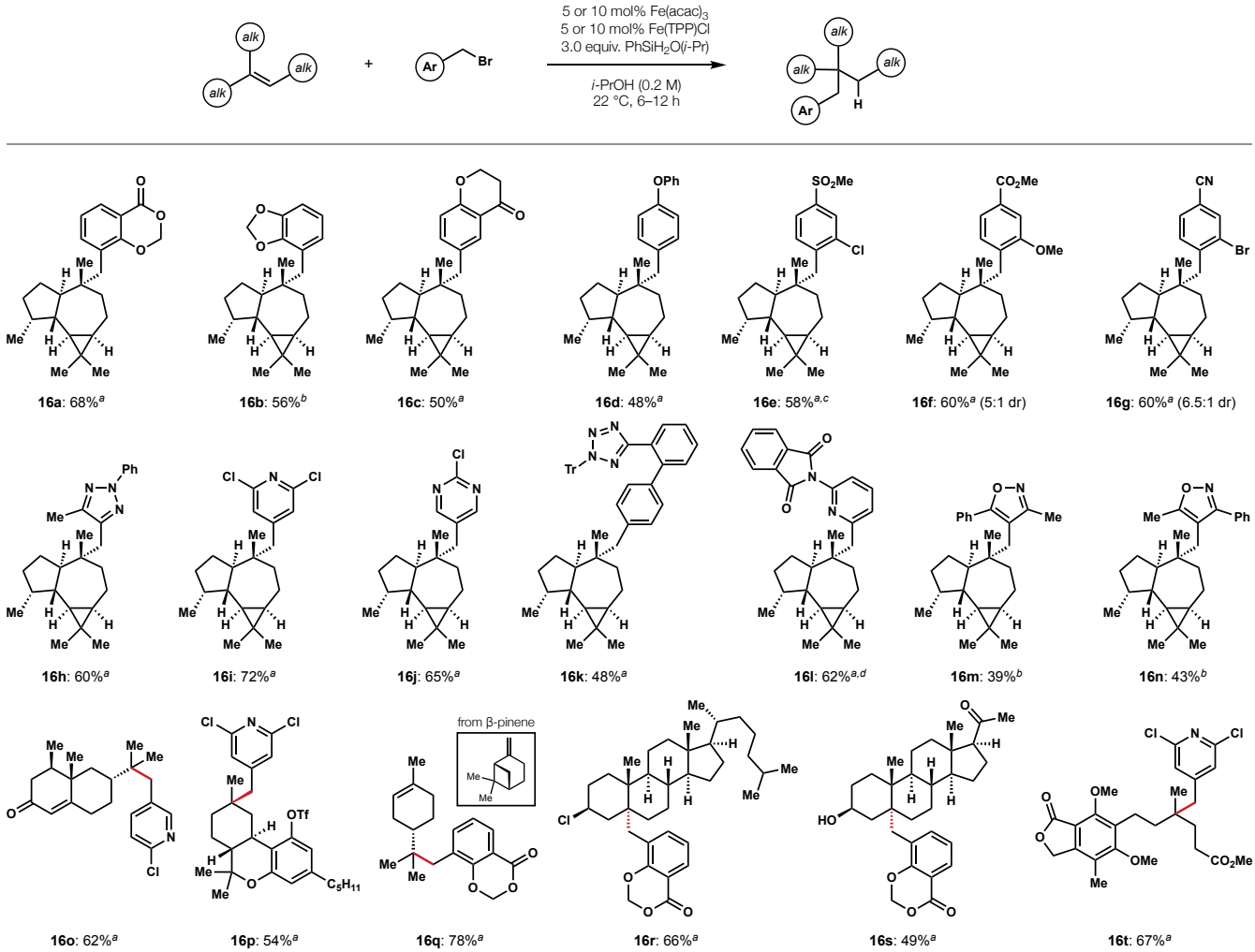


Table 2. Preliminary scope of iron-catalyzed hydrobenzylation via MHAT/S_H2. All reactions conducted with 0.2 mmol of alkene and 0.1 mmol of benzyl bromide; diastereomeric product ratios >10:1 unless otherwise noted. [a] 5 mol% $Fe(acac)_3$ and 5 mol% Fe(TPP)Cl; [b] 10 mol% $Fe(acac)_3$ and 10 mol% Fe(TPP)Cl; [c]solvent = 4:1 *i*-PrOH/acetone; [d]solvent = 1:1 *i*-PrOH/acetone.

restricted scope of our first-generation Mn/Ni hydrobenzylation. In addition to complex sesquiterpenes like aromadendrene (**3**) and $\Delta^{3',4'}$-dehydro-globulol (**2**, see Scheme 1), nootkatone (to **16o**) and a Δ^8-tetrahydrocannabinoid derivative (to **16p**) coupled efficiently with pyridylmethyl bromides. Monoterpenes like pinene (to **16q**), complex steroids like cholesteryl chloride (see **16r**) and pregnenolone (to **16s**), and meroterpenoids like *O*-methyl methyl mycophenolate (to **16t**) were also productive substrates. In this latter case, the alkene could isomerize into conjugation with both the arene and the ester, but the S_H2 reaction outcompetes these reactions, which would likely be mediated by HAT to $(TPP)Fe^{2+}$.

The proposed, intersecting catalytic cycles are depicted in Figure 2 (for a longer discussion, see SI). The alkene is likely to undergo MHAT with a fleeting metal hydride generated from silane and $Fe(acac)_3$; the low-BDE Fe^{3+}–H is thought to react[11d] at the hextet spin state[11c] and prefer outer-sphere MHAT over an inner-sphere coordination/migratory insertion,[11] driven by the weak-field β-diketonate ligands.[36,11c,11d] The resulting tertiary carbon radical (R_3C•) can either undergo equilibrium collapse to a *tert*-alkyl organoiron[11,37] (R_3C–Fe^{3+}) or engage the benzyliron(TPP) complex directly.[12] The benzyliron(TPP) is likely to form by capture of benzyl radical (Bn•) by $(TPP)Fe^{2+}$, which may itself form via hydrogen evolution from 2 $(TPP)Fe^{3+}$–H or the proposed S_H2 reaction. The origin of Bn• is unclear but control experiments suggest its formation by both $(TPP)Fe^{3+}$–H and $(acac)_2Fe^{3+}$–H by analogy to Leonori's HAT/XAT mechanism (see SI).[38] We did not observe any reaction of the BnBr with $(TPP)Fe^{2+}$. We consider S_H2 more likely than persistent radical effect (PRE)-driven heterodimerization because of the low dr (1:1) associated with background coupling in the absence of Fe(TPP)Cl (Table 1, entry 4), low dr

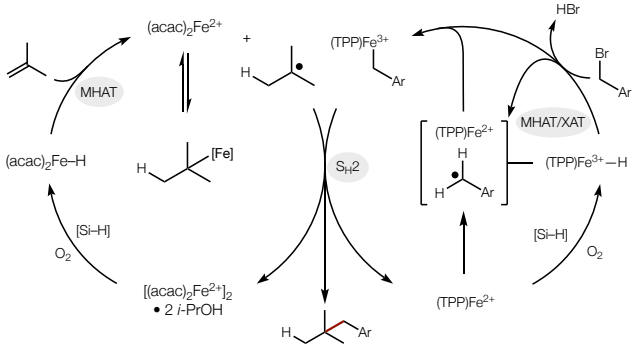


Figure 2. Proposed intersection of catalytic cycles. See text for competing hypotheses.

in the variations to our 1st generation hydrobenzylation conditions,[39] and the precedent of Ref. 12–16. These data suggest

Figure 5 as a likely dual catalytic cycle, but further interrogation is required to clarify numerous features of this reaction.

Eugenial C and its analogs are now available by a modular route that relies on an iron-catalyzed alkene/benzyl bromide cross-coupling through a putative MHAT/S_H2 sequence, the first of its kind. This terpene hydrobenzylation transform differs significantly from prior disconnections to access terpenephenolic meroterpenoids[40] and may prove generally simplifying. For example, symmetric partner **9** allows for late-stage diversification after coupling with diverse alkenes like chiral pool terpenes. Whether the arene primarily undergoes redox reactions, disrupts membranes[41] and/or adducts lysines through its salicylaldehyde[42] and whether the terpene serves as a lipophilic vehicle[43] or binds a hydrophobic pocket can now be interrogated by synthesis. The iron-catalyzed cross-coupling offers a new jumping-off point for the development of a suite of branched-selective alkene hydrofunctionalizations that obviate the need for nickel, whose toxicity can present problems for large-scale pharmaceutical applications.[44] Numerous paths are now made available through this study in natural product synthesis.

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).
X-ray structure reports (PDF)
X-ray structure files (CIF)

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