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Communication

Engaging Alkenes in Metallaphotoredox: A Triple Catalytic, Radical Sorting Approach to Olefin-Alcohol Cross-Coupling

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ABSTRACT: Metallaphotoredox cross-coupling is a well-established strategy for generating clinically privileged aliphatic scaffolds via single-electron reactivity. Correspondingly, expanding metallaphotoredox to encompass new C(sp^3)-coupling partners could provide entry to a novel, medicinally relevant chemical space. In particular, alkenes are abundant, bench-stable, and capable of versatile C(sp^3)-radical reactivity via metal-hydride hydrogen atom transfer (MHAT), although metallaphotoredox methodologies invoking this strategy remain underdeveloped. Importantly, merging MHAT activation with metallaphotoredox could enable the cross-coupling of olefins with feedstock partners such as alcohols, which undergo facile open-shell activation via photocatalysis. Herein, we report the first C(sp^3)−C(sp^3) coupling of MHAT-activated alkenes with alcohols by performing deoxygenative hydroalkylation via triple cocatalysis. Through synergistic Ir photoredox, Mn MHAT, and Ni radical sorting pathways, this branch-selective protocol pairs diverse olefins and methanol or primary alcohols with remarkable functional group tolerance to enable the rapid construction of complex aliphatic frameworks.

Within organic synthesis, cross-coupling technologies have profoundly streamlined the preparation of complex, high-value molecules across numerous chemical industries.[1] Notably, metallaphotoredox cross-coupling harnesses reactive radical intermediates under mild, transition-metal-mediated bond-forming conditions.[2] By enabling open-shell functionalization of abundant feedstocks, such as amines, carboxylic acids, and C−H nucleophiles, metallaphotoredox catalysis allows fragment couplings that would be unachievable via traditional two-electron pathways.[3−6] These transformations are particularly suited for delivering C(sp^3)-rich scaffolds, molecular cores increasingly recognized as vital components of clinically successful small molecule drug candidates (Figure 1a).[7,8] Novel metallaphotoredox methods, particularly those employing new aliphatic partners and allowing previously untenable retrosynthetic disconnections, have the potential to provide access to unexplored, medicinally relevant chemical space.[9]

To this end, a central goal in metallaphotoredox has been the incorporation of underutilized yet advantageous C(sp^3)-radical progenitors within open-shell cross-coupling systems.[2] Among many possibilities, our laboratory recently identified olefins as a nontraditional motif that might be activated for metallaphotoredox fragment couplings. Alkenes, which are naturally occurring or readily accessible from ubiquitous precursors (e.g., halides, alcohols, carbonyls),[10] represent a structurally varied, bench-stable substrate class that is highly commercially available compared to traditional electrophilic and organometallic reagents (Figure 1b).[11] However, beyond their deployment as "conjunctive" linchpins for specific multicomponent reactions, olefins have seen limited consideration as partners for directing group-free, C(sp^3)-enriching metallaphotoredox couplings.[12,13] If simpler alkene-to-C(sp^3)-radical activation modes (primarily those more reminiscent of "conventional" cross-coupling logic)[14] could be employed in metallaphotoredox, pharmaceutically valuable linkages such as C−C bonds could be delivered through predictable and expedient synthetic routes. Moreover, by pairing olefins with other photoredox-compatible feedstock substrates, a range of convenient but otherwise inaccessible C(sp^3)−C(sp^3) fragment couplings may be realized under mild conditions.[3] Specifically, an alkene might be induced to undergo metallaphotoredox cross-coupling with a transient radical species derived from an alcohol substrate. To this end, we have developed an *N*-heterocyclic carbene (NHC)-mediated alcohol deoxygenation platform that can be harnessed for the direct C(sp^3)−C(sp^3) coupling of alcohols with acid or halide partners.[13a,15,16] In light of the structural variance and commercial abundance of alcohols,[11] we expect that a direct alcohol−alkene cross-coupling could permit single-step exploration of vast aliphatic chemical diversity.

Given that olefin π-systems can furnish sp^3-based radical intermediates through various open-shell pathways, it was necessary to devise an appropriate alkene-to-radical activation strategy at the outset. Metal-hydride hydrogen atom transfer (MHAT) is capable of generating radicals via simple C−H bond-forming events and thus represents a chemoselective and retrosynthetically appealing approach to Markovnikov-selective radical production from unactivated olefins.[17] Using sustainable metals—such as Co, Fe, and Mn—MHAT hydrofunctionalization catalysis has enabled Mukaiyama hydrations, Giese additions, azidations, aminations, and even olefin-based cross-

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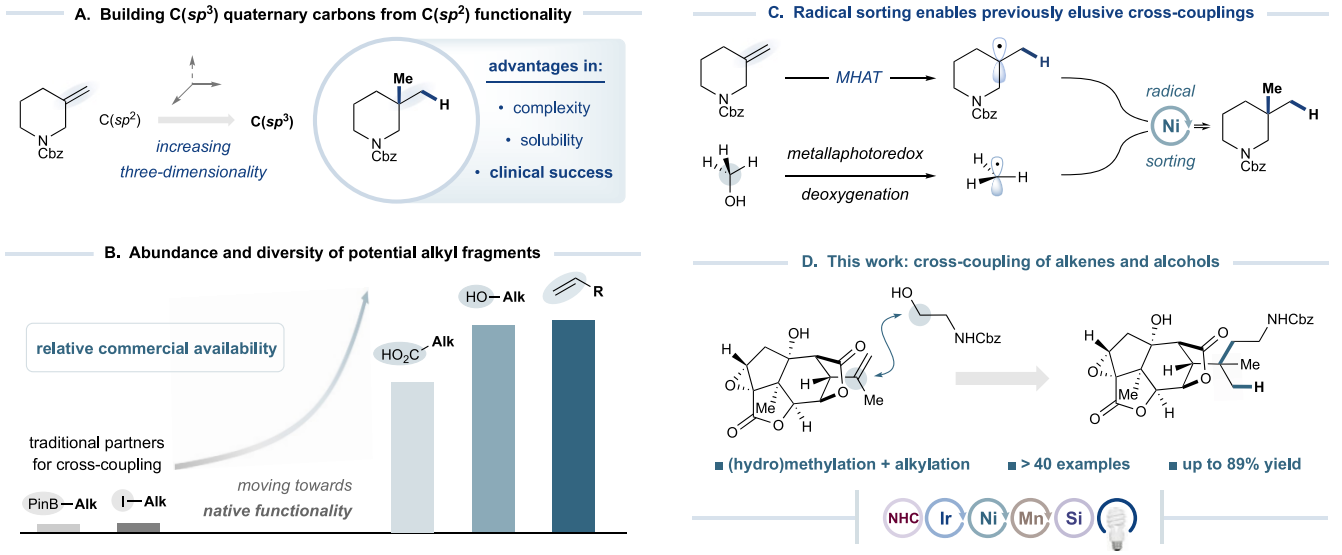

Figure 1. Metallaphotoredox olefin-alcohol cross-coupling.

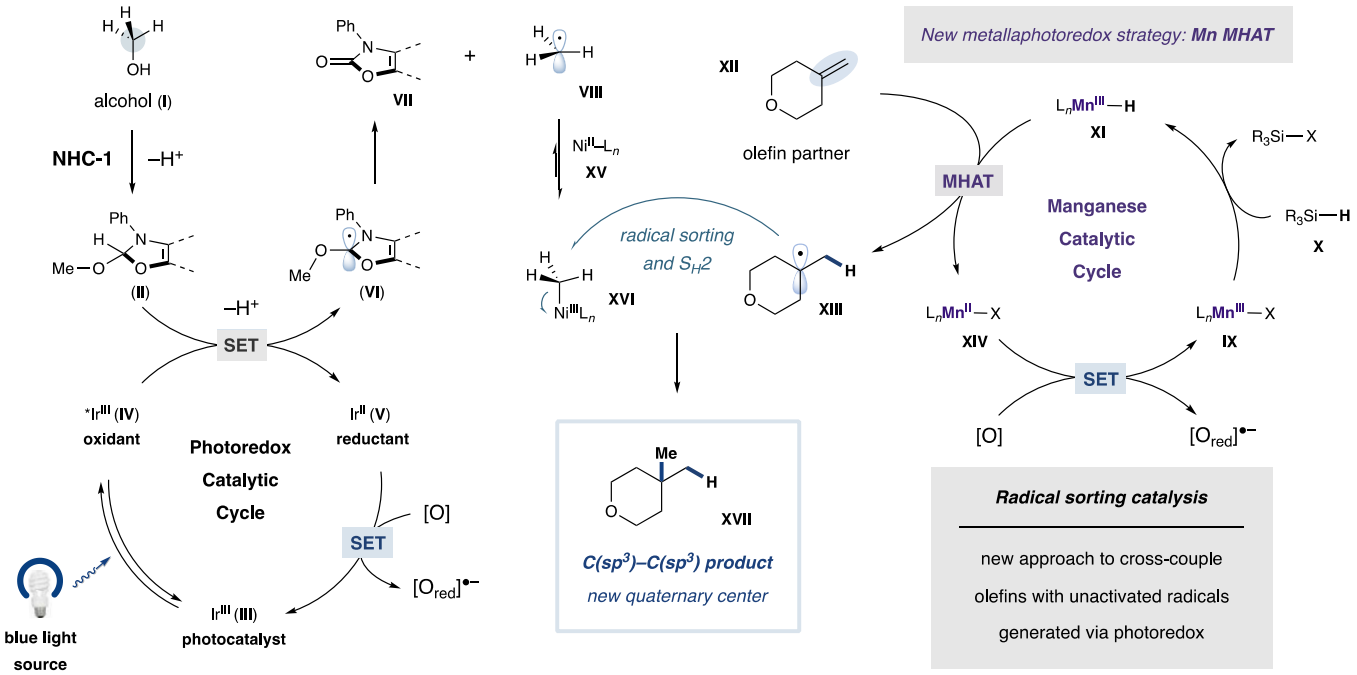

Figure 2. Plausible mechanism for olefin-alcohol cross-coupling.

couplings under thermal activation.[18,19] Drawing from these precedents, we proposed achieving the envisioned alkene–alcohol cross-coupling by merging MHAT-based alkene activation with NHC-mediated alcohol deoxygenation (Figure 1c).[15] However, the success of such a method would require hindered secondary and tertiary radicals, accessed via MHAT from common olefin substitution patterns, to undergo facile bond formation with alcohol-derived unstabilized radicals. Despite numerous advances in MHAT reactivity,[17] this specific type of dual radical cross-coupling has remained underdeveloped,[20] consistent with energetic challenges for inner-sphere reductive elimination at metal centers when using hindered radical partners.[21,22]

To achieve selective open-shell cross-coupling of alcohols and olefins (Figure 1d), we sought to leverage "radical sorting" catalysis, which has been recently deployed in our laboratory and others.[15b,f,23−25] Under this biomimetic strategy, two carbon-centered radicals with differing substitution patterns are thermodynamically distinguished by a high-valent metal catalyst, wherein the less substituted methyl or primary radicals are preferentially captured by the metal center.[24b] The remaining transient nucleophilic (often tertiary) radicals can engage in *outer-sphere* bond-forming processes with the nascent and persistent electrophilic metal–alkyl intermediate.[26,27] Following bimolecular homolytic substitution (S_H2) principles,[25] these events readily furnish congested motifs, including quaternary centers, while achieving cross-selectivity via "radical sorting" as dictated by metal-binding favorability and S_H2 kinetics.[23] While related Fe-mediated MHAT couplings are known in thermal contexts,[20] our success in pairing unstabilized radicals via Ni(scorpionate),[13,24] Ni(diketonate),[15b] and Fe(porphyrin)[15f,23] sorting platforms suggested that metallapho-

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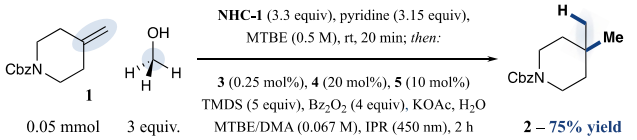
toredox could be remarkably adaptable to radical sorting with olefins and alcohols. Importantly, the synergistic use of photoredox, MHAT, and radical sorting strategies would mandate careful, coordinated optimization of each catalytic cycle, a requirement made less burdensome by the plethora of sorting catalysts available within metallaphotoredox settings.[2,23−25] Herein, we report a successful platform for olefin-alcohol coupling—formally a "deoxygenative hydroalkylation"—based on this mechanistic blueprint that expediently delivers C(sp^3)-complexity through the coordinated action of Ir/Mn/Ni triple cocatalysis under photonic activation.

Figure 2 details a plausible olefin−alcohol cross-coupling mechanism that merges (a) NHC-mediated alcohol activation, (b) MHAT-based olefin activation, and (c) radical sorting for heteroselective bond formation. Prior to irradiation, an alcohol substrate (i.e., methanol, **I**) first condenses with a benzoxazolium salt (termed "**NHC-1**") to form activated NHC−alcohol adduct **II**.[15] Subsequently, excitation and intersystem crossing of a suitable Ir(III) photocatalyst (**III**) under blue light irradiation could generate a long-lived and oxidizing triplet excited state **IV**.[28] As established previously,[15] adduct **II** can initiate reductive quenching with **IV** via single-electron transfer (SET), which provides reduced Ir(II) photocatalyst **V** and, after deprotonation, carbon-centered radical **VI**. Critically, this unique intermediate undergoes facile β-scission and liberation of both a stable carbamate byproduct (**VII**) and the desired methyl radical (**VIII**). Concurrently, transmetalation between Mn(III) MHAT (pre)catalyst **IX** and hydrosilane reagent **X** affords Mn−H intermediate **XI**.[17] Ensuing MHAT between **XI** and olefin **XII** would furnish tertiary radical **XIII** and the Mn(II) intermediate **XIV**. With reduced forms of the photocatalyst and MHAT catalyst now present, we anticipated that mild exogenous oxidants could promote SET events that regenerate both ground-state Ir(III) photocatalyst **III** and starting MHAT catalyst **IX**.[29,30] Lastly, in the crucial coupling event between radicals **VIII** and **XIII**, Ni(II) sorting catalyst **XV** would preferentially capture the less substituted methyl radical, thereby delivering persistent Ni(III)−methyl species **XVI**. Free tertiary radical **XIII** could then undergo S_H2 displacement with complex **XVI**,[23−25] affording C(sp^3)−C(sp^3) cross-coupled product **XVII** while regenerating Ni catalyst **XV**.[31]

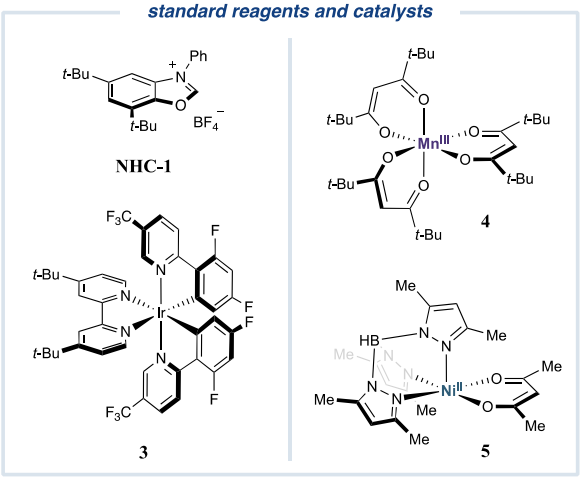
Recognizing the importance of the "magic methyl effect" in pharmaceutical design, we first evaluated our proposed olefin−alcohol coupling for deoxygenative hydromethylation using alkene **1** and methanol as a widely available yet nontraditional methylating agent (Table 1; see Supporting Information (SI) for details).[32] Delightfully, quaternary product **2** was obtained in 75% yield using Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (**3**; τ = 2.3 μs; $E_{1/2}^{red}[*Ir^{III}/Ir^{II}]$ = +1.21 V vs SCE in MeCN)[28] as a photocatalyst under standardized 450 nm Integrated Photoreactor (IPR) irradiation (entry 1).[33] These optimal conditions also featured hydrosilane reagent 1,1,3,3-tetramethyldisiloxane (TMDS), benzoyl peroxide as a mild oxidant, Mn(dpm)$_3$ (**4**, dpm = dipivaloylmethane) for MHAT activation, and Ni-scorpionate catalyst **5** (formed *in situ* from Ni(acac)$_2$ and trispyrazolylborate ligand KTp*)[24] for radical sorting (Figure 2), alongside beneficial base and water additives (entries 2 and 3).[34] As outlined in Table 1, judicious catalyst selection proved essential for reactivity.[2,17] For the radical sorting step, product **2** was obtained in minimal yield using Fe-based catalysts[15f,20,23] or in the absence of sorting conditions (entries 4 and 5). By contrast, diketone- and KTp*-ligated Ni complexes—which are known to promote radical sorting reactivity—were each

Table 1. Optimization and Control Reactions[a]



entry	deviation	yield[b]
1	none	75%
2	in absence of base (KOAc)	65%
3	in absence of H_2O additive	65%
4	Fe(OEP)Cl instead of **5**	2%
5	no Ni catalyst **5**	10%
6	Ni(acac)$_2$ instead of **5**	67%
7	Fe(acac)$_3$ instead of **4**	9%
8	Co(acac)$_2$ or Co(salen) instead of **4**	4%
9	no Mn catalyst **4**	0%
10	no light	5%
11	no photocatalyst **3**	19%
12	no TMDS	0%
13	no oxidant	0%

[a]Typically performed with 0.5 equiv. KOAc, 5 equiv. H_2O and 4:1 MTBE/DMA. See SI for experimental details. [b]Yield determined by ^{1}H NMR. Ac, acetyl; Acac, acetylacetonate; Bz, benzoyl; Cbz, benzyloxycarbonyl; DMA, N,N-dimethylacetamide; MTBE, methyl *tert*-butyl ether; OEP, 2,3,7,8,12,13,17,18-octaethyl-21H,23H-porphine.



effective in some capacity (entry 6).[15b,24] Moreover, Mn-catalyzed olefin activation emerged as a privileged option over Fe−H, Co−H, and MHAT-free systems (entries 7−9).[17] When considering the various Mn, Fe and Co complexes suitable for MHAT, different catalysts may show distinct thermodynamic capacities to compete with Ni for methyl radical capture,[35] behavior consistent with open-shell formation of metal−alkyl intermediates in previous MHAT systems.[36] Beyond differences in redox potentials, we hypothesize that the chosen Mn catalyst effectively avoids radical capture and off-cycle Mn−methyl formation, instead favoring productive Mn(III)−H activity.[17,35] These unique advantages of synergistic Ir/Mn/Ni triple catalysis for olefin activation and radical sorting are an emerging topic that will be addressed in subsequent studies.[31] Lastly, additional control reactions demonstrated that blue light, photocatalyst, hydrosilane, and oxidant were required for sufficient reactivity (entries 10−13), consistent with the metallaphotoredox-MHAT mechanistic blueprint outlined in Figure 2.[37,38]

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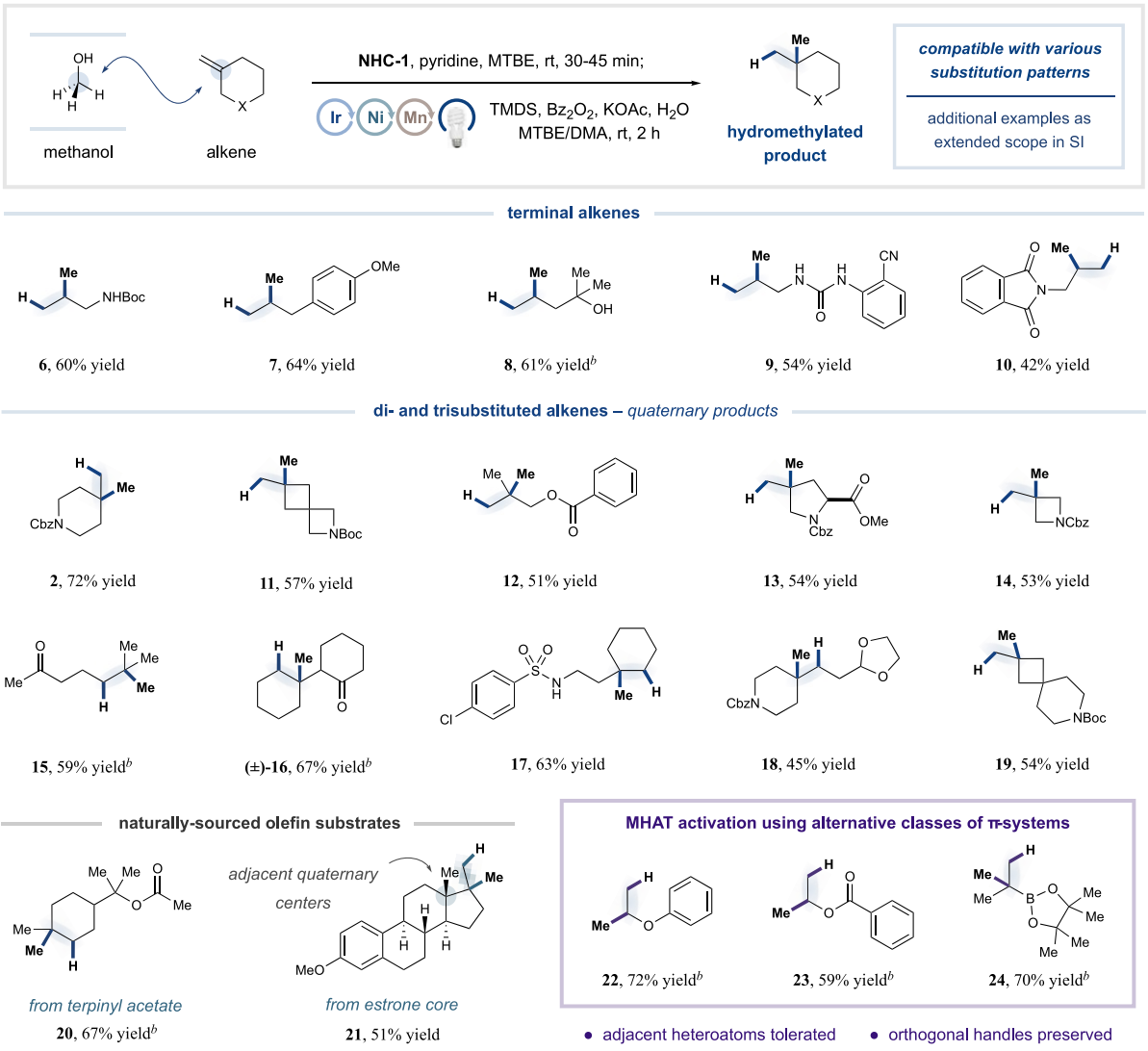
Table 2. Alkene Scope for Methanol-Enabled Hydromethylation[a]



[a]Typically performed using methanol (3 equiv), **NHC-1** (3.3 equiv), pyridine (3.15 equiv) in MTBE (0.50 M) for 30−45 min, then alkene (0.5 mmol, 1 equiv), **3** (0.25 mol %), **4** (20 mol %), **5** (10 mol %), TMDS (5 equiv), Bz_2O_2 (4 equiv), KOAc (0.5 equiv), H_2O (5 equiv) and MTBE/DMA (4:1, 0.067 M), under IPR irradiation (450 nm) for 2 h. All yields isolated unless noted otherwise. See SI for experimental details. [b]Yield determined by ^{1}H NMR (due to volatility/instability). Boc, *tert*-butoxycarbonyl.

With optimal conditions in hand, we next evaluated the alkene scope for this transformation. To our delight, Markovnikov hydromethylation was achievable with a full branched selectivity across a range of alkene substitution patterns (Table 2). Notably, while terminal olefins furnish modestly nucleophilic secondary radicals upon MHAT activation,[17,26] these intermediates consistently underwent facile radical sorting to deliver hydromethylated products (**6**−**10**, 42−64% yield). Additionally, substrates bearing hindered di- or trisubstituted alkenes were readily leveraged as tertiary radical precursors via MHAT. This extension resulted in products containing quaternary centers (**2** and **11**−**19**, 45−72% yield), motifs that remain elusive under many typical cross-coupling conditions.[21,22] Given the absence of low-valent Ni intermediates (e.g., Ni(0) species) in Ni(II)/Ni(III) radical sorting platforms,[15b,24] a selection of functional groups typically sensitive to oxidative addition, including allylic carboxylates and aryl halides, are chemoselectively tolerated in all cases.[39] Moreover, several naturally sourced terpenoid- and hormone-derived substrates were competent within this protocol (**20** and **21**, 67% and 51% yield, respectively), furnishing congested motifs (including contiguous quaternary carbons) in short order. Beyond traditional "unactivated" alkenes, deoxygenative hydromethylation could be extended to heteroatom-bearing π-partners (**22**−**24**, 59−72% yield), a finding that may inform C(sp^3)-enriching coupling sequences via exploitation of retained orthogonal functionality (i.e., boronic esters).[40] Overall, this protocol affords medicinally valuable gem-dimethyl, methylcycloalkyl, and quaternary units from diverse olefins,[41] all while using a bulk solvent (methanol) as an atypical methylating reagent.[42]

To probe the versatility of this new technology, we next investigated the scope of alcohols amenable to deoxygenative hydroalkylation (Table 3). Using Ni(diketonate) sorting catalysts,[15b] an array of primary substrates were readily paired with hindered olefins to provide direct access to quaternary centers (see SI for additional hydroalkylation examples).[42] Gratifyingly, ethanol and ether-, acetal-, or ketone-containing alcohol substrates were broadly successful (**25**−**31**, 51−74%

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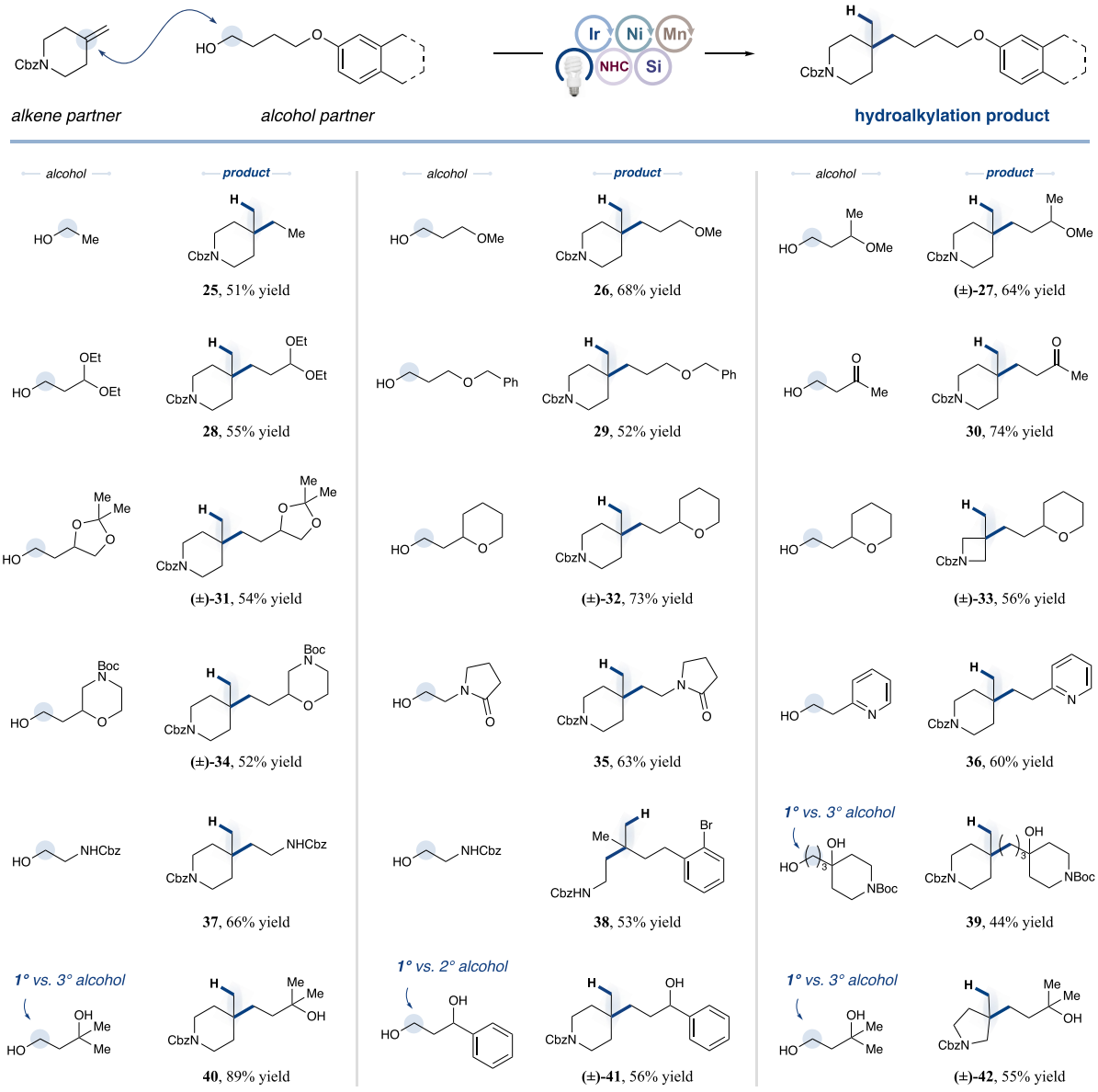
Table 3. Alcohol Scope for Deoxygenative Hydroalkylation[a]



[a]Isolated yields reported. See SI for experimental details.

yield), as were substrates bearing tetrahydropyran (**32** and **33**, 73% and 56% yield, respectively), morpholine (**34**, 52% yield), lactam (**35**, 63% yield), or pyridine (**36**, 60% yield) heterocyclic functionality. Moreover, the functional group tolerance of this method allowed for retention of protic motifs, such as amine derivatives and unprotected distal alcohols (**37**−**42**, 44−89% yield). This finding is significant given that sequential, site-selective diol deoxygenations are well-established using **NHC-1**;[15] as such, MHAT-olefin coupling may represent a practical entry point toward elaborating native polyols into complex alkylated scaffolds.

Lastly, to rapidly produce drug-like molecular architecture from native functionality,[7−9] we harnessed olefin−alcohol coupling for the late-stage derivatization of therapeutic scaffolds. Using a selection of commercial alcohols, diverse C(sp^3)-rich products were furnished directly from bioactive compounds bearing pendant olefins (Table 4). Through the hydroalkylation of antibiotics, antihypertensives, stimulants, steroids, and muscular dystrophy or hyperuricemia medications, this approach delivered a series of novel and potentially efficacious drug analogues amenable to further evaluation (**43**−**50**, 30−74% yield). Across all cases, the unique tolerance of this method for labile functionality—including epoxides, oxidation-sensitive amines or sulfides, coordinating alcohols or heteroarenes, and oxidative addition-prone 1,2,4-oxadiazoles[4a,43−45]—was critical for generating complex molecular architecture efficiently.

Collectively, these examples underscore the utility, expediency, and selectivity offered by metallaphotoredox olefin−alcohol coupling in the construction of aliphatic scaffolds of medicinal relevance. Moreover, we envision that synergistic Ir/Mn/Ni triple cocatalysis can be generically advantageous for C(sp^3)−C(sp^3) bond formations between olefins and various radical partners. As such, further mechanistic evaluation and application of this photocatalytic platform will be reported in due course.

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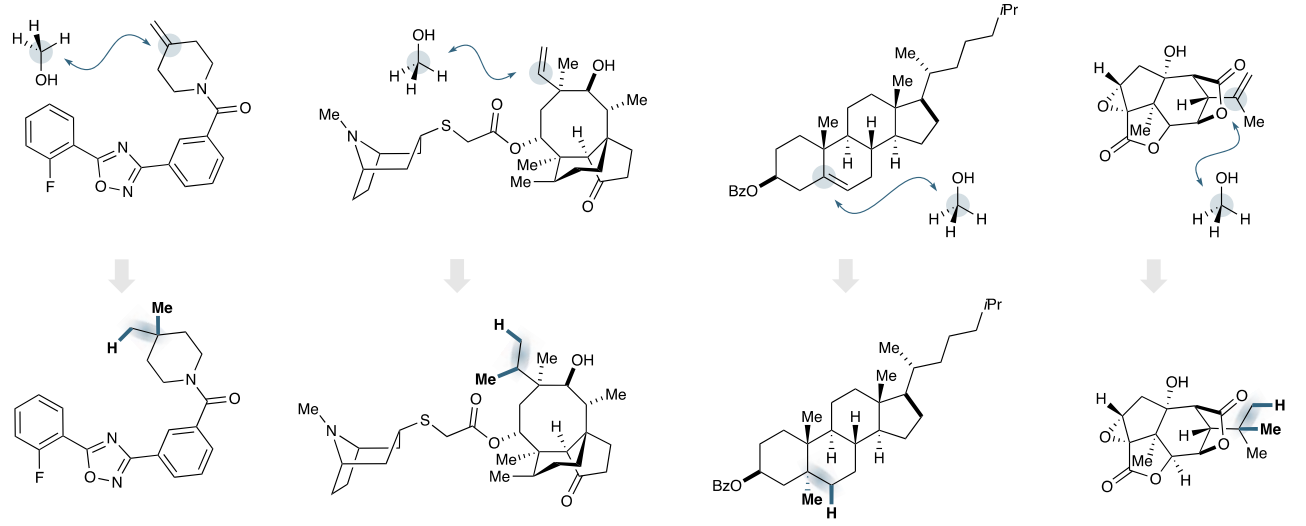
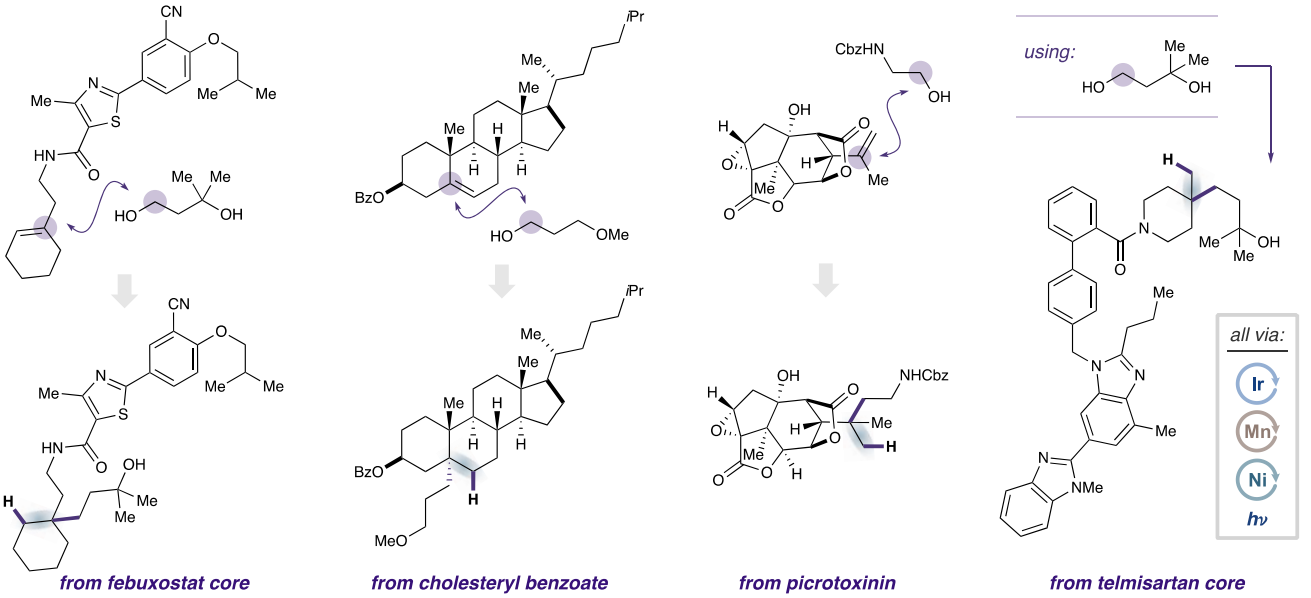
Table 4. Hydroalkylation of Bioactive Compounds[a]

late-stage hydromethylation



from ataluren core	*from retapamulin*	*from cholesteryl benzoate*	*from picrotoxinin*
(muscular dystrophy)	*(pleuromutilin antibiotic)*	*(steroid derivative)*	*(stimulant/convulsant)*
43, 51% yield	**44**, 30% yield	**45**, 74% yield[b]	**46**, 51% yield

late-stage hydroalkylation



from febuxostat core	*from cholesteryl benzoate*	*from picrotoxinin*	*from telmisartan core*
(hyperuricemia treatment)	*(steroid derivative)*	*(stimulant/convulsant)*	*(hypertension treatment)*
47, 60% yield	**48**, 70% yield[b]	**49**, 34% yield	**50**, 64% yield

[a]All yields isolated unless noted otherwise. See SI for experimental details. [b]Yield determined by ^{1}H NMR.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c02316.

Experimental details, expanded substrate table, compound characterization data, and spectra (PDF)

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Notes

The authors declare the following competing financial interest(s): D.W.C.M. declares a competing financial interest with respect to the Integrated Photoreactor.

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