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

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Supporting Information Placeholder

ABSTRACT: Metallaphotoredox cross-coupling is a well-established strategy for generating clinically privileged aliphatic scaffolds via open-shell reactivity. The introduction of new C(sp^3)-coupling partners within this paradigm can provide entry to novel, medicinally-relevant chemical space. Alkenes are abundant, bench-stable and undergo facile C(sp^3)-radical reactivity via metal-hydride hydrogen atom transfer (MHAT), yet metallaphotoredox methodologies invoking this strategy remain underdeveloped. Importantly, the merger of MHAT activation with metallaphotoredox catalysis could enable cross-coupling of olefins with feedstock radical partners only activated via photocatalysis, such as alcohols. Herein, we report the first C(sp^3)–C(sp^3) coupling of MHAT-activated alkenes with alcohols (i.e. deoxygenative hydroalkylation) via triple co-catalysis. Through synergistic Ir photocatalysis, Mn MHAT and Ni radical sorting pathways, this branch-selective protocol pairs diverse olefins with methanol or primary alcohols, displays remarkable functional group tolerance, and enables the rapid construction of complex aliphatic frameworks.

In the realm of organic synthesis, cross-coupling technologies have profoundly streamlined the preparation of complex, high-value molecules across numerous chemical industries.[1,2] Notably, the metallaphotoredox cross-coupling platform harnesses reactive radical intermediates under mild, transition metal-mediated bond-forming conditions.[3] By enabling open-shell functionalization of abundant yet conventionally inert aliphatic feedstocks such as chlorides, carboxylic acids and C–H nucleophiles, this powerful strategy enables practical fragment couplings unachievable via traditional two-electron pathways.[4–7] These transformations are particularly suited for delivering C(sp^3)-rich scaffolds, molecular cores which are increasingly recognized as vital components of clinically successful small molecule drug candidates (**Figure 1**).[8] Novel metallaphotoredox methods, particularly those employing new aliphatic partners and offering previously untenable retrosynthetic disconnections, can ultimately provide valuable approaches to unexplored, medicinally-relevant chemical space.

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.[3] Among many possibilities, we recently identified olefins as an ideal, non-traditional motif to activate for metal-based fragment couplings via photoredox. Alkenes, which are naturally occurring

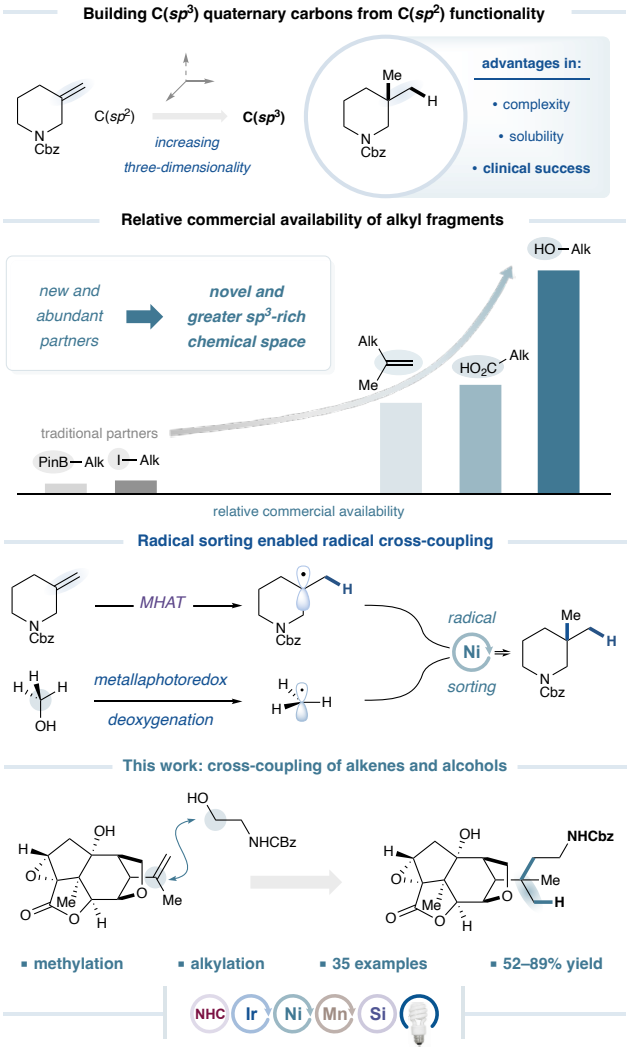


Figure 1: Cross-coupling of alcohols and alkenes.

or readily furnished from halide, alcohol, and carbonyl precursors, represent a structurally varied, bench-stable substrate class far more commercially accessible than traditional electrophilic and organometallic reagents (**Figure 1**).[9–11] However, beyond their use as "conjunctive" linchpins for highly specific multicomponent reactions,[12,13] olefins have seen limited consideration as partners for direct, C(sp^3)-enriching metallaphotoredox couplings. If simpler alkene-to-C(sp^3)-radical activation modes

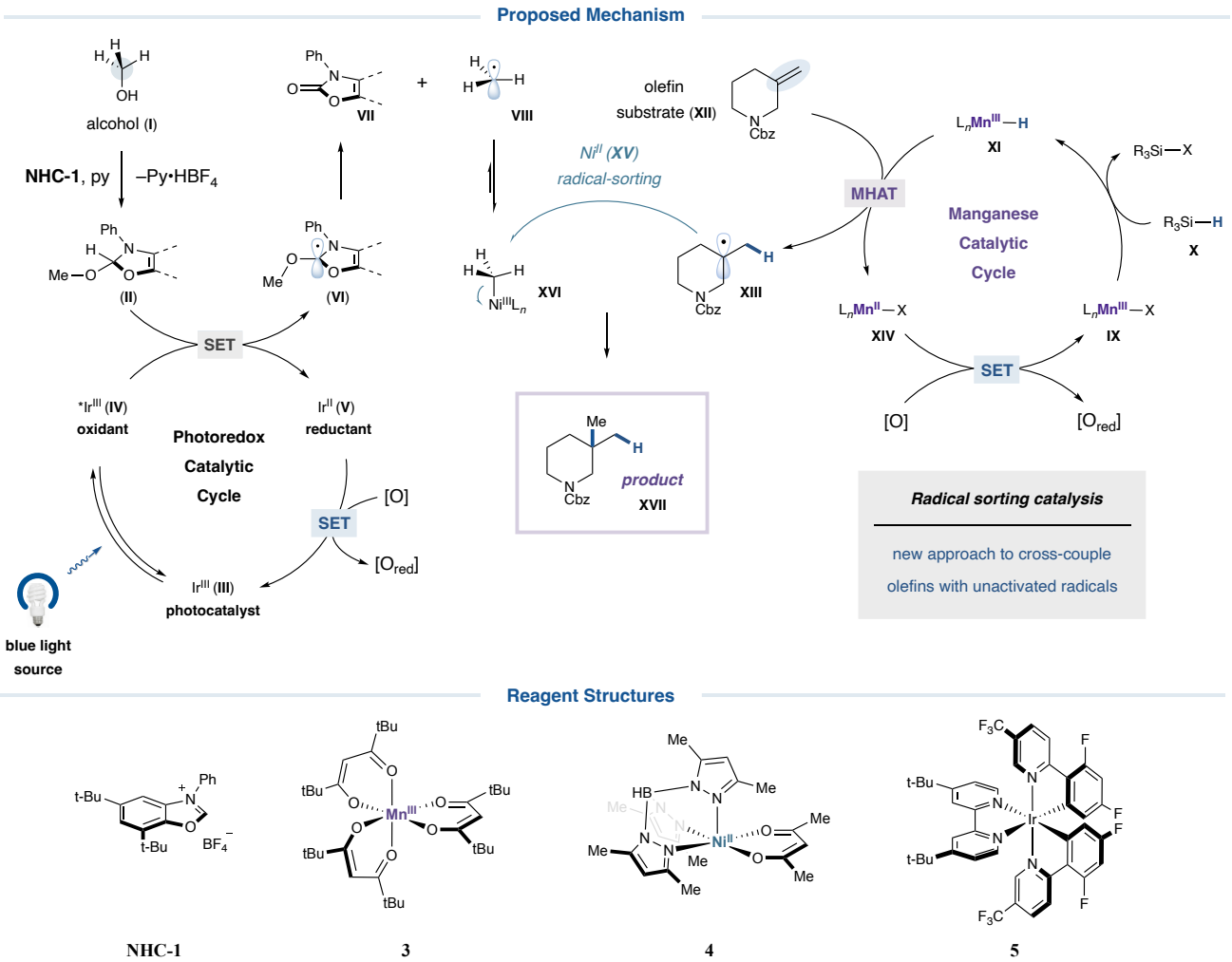


Figure 2. Plausible mechanism and reagent structures for metallaphotoredox olefin-alcohol coupling.

(primarily those more reminiscent of "conventional" cross-coupling logic) could be employed in metallaphotoredox, pharmaceutically valuable linkages such as C–C bonds could be accessed through predictable and expedient synthetic routes.[14] Moreover, by pairing olefins with other feedstock substrates only activated via photoredox, a range of convenient but otherwise inaccessible C(sp^3)–C(sp^3) fragment couplings may be realized under mild conditions.[3] As one example, metallaphotoredox alkene cross-couplings could feature alcohols as the second partner, based on our laboratory's advances in open-shell reactivity with this native functional group via *N*-heterocyclic carbene (NHC)-mediated deoxygenation.[15,16] When considering the structural diversity and commercial abundance attributed to alcohols (even relative to olefins; **Figure 1**),[11] this ideal pairing would permit single-step exploration of vast aliphatic chemical space previously undeveloped within medicinal chemistry contexts.

Given that olefin π-systems can react to furnish sp^3-based radical intermediates through various open-shell pathways, the selection of one ideal alkene-to-radical activation strategy is critical from the outset. Based on its utility for radical generation via simple C–H bond-forming events, metal-hydride hydrogen atom transfer (MHAT) represents a chemoselective and retrosynthetically-appealing approach to Markovnikov-selective radical production from unactivated olefins.[16,17] 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-couplings under thermal activation.[18,19] These examples suggest that MHAT could be deployed for advantageous cross-couplings through a merger with NHC-mediated alcohol deoxygenation, a photoredox platform harnessed previously for C(sp^3)–C(sp^3) couplings with acid or halide radical partners (**Figure 1**).[15] However, for such a methodology to flourish, the hindered secondary and tertiary radicals available from common olefin substitution patterns via MHAT must undergo facile bond-forming events with alcohol-derived unstabilized radicals. Despite numerous advances in MHAT reactivity,[16] this specific type of dual radical cross-coupling has remained underdeveloped, consistent with energetic challenges for inner-sphere reductive elimination at metal centers when using hindered radical partners.[20,21]

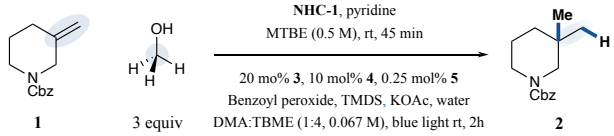
Accordingly, we became inspired by recent advances in our laboratory and others regarding "radical sorting" catalysis, a unique mechanism that could accomplish this challenging open-shell coupling of olefins and alcohols (**Figure 1**).[15, 22–24] Under such conditions, two carbon-centered radicals of differing substitution are distinguished by a high-valent metal catalyst on thermodynamic grounds, wherein less substituted methyl or primary radicals are preferentially captured by the metal

center.[22] This biomimetic strategy leaves behind transient nucleophilic (often tertiary) radicals that engage in *outer-sphere* bond-forming processes with the nascent electrophilic metal–alkyl intermediate. This bimolecular homolytic substitution (S_H2) event readily furnishes congested motifs such as quaternary centers while achieving cross-selectivity via "radical sorting" as dictated by metal-binding favorability and S_H2 kinetics.[22] While related Fe-mediated MHAT couplings are known in thermal contexts,[16] our success pairing unstabilized radicals via Ni-scorpionate,[23,24] Ni-diketonate[15b] and Fe-porphyrin[15e] sorting platforms suggested that metallaphotoredox may be remarkably adaptable towards performing radical sorting with olefins and alcohols. In particular, our envisioned use of synergistic photoredox, MHAT and radical sorting strategies would mandate careful and intertwined optimization of each catalytic cycle, a requirement made less burdensome by the plethora of sorting catalysts available within metallaphotoredox settings.[23–25] Herein, we report the successful development of an olefin-acid cross-coupling (formally a "deoxygenative hydroalkylation") based on this mechanistic blueprint, a method that readily builds C(sp^3)-complexity through the coordinated action of Ir/Mn/Ni triple co-catalysis under photonic activation.

Based on the anticipated requirements for open-shell olefin-alcohol cross-coupling described above, **Figure 2** details our envisioned 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**) condenses with benzoxazolium salt **NHC-1** to form the activated NHC−alcohol adduct (**II**) under moderately basic conditions.[15] Subsequently, excitation and intersystem crossing of Ir(III) photocatalyst Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (**III**) under blue light irradiation leads to formation of the long-lived ($\tau = 2.3$ μs) and oxidizing triplet excited state **IV** ($E_{1/2}^{red}[*Ir^{III}/Ir^{II}]$ = +1.21 V vs SCE in MeCN).[26] As established previously,[15] adduct **II** can readily initiate reductive quenching with **IV** via single-electron transfer (SET) to provide reduced Ir(II) photocatalyst **V**. Simultaneously, deprotonation of the amine radical cation generated via oxidation of **II** would deliver carbon-centered radical **VI**, an intermediate prone to facile β-scission and liberation of both a stable carbamate byproduct (**VII**) and the desired methyl radical (**VIII**). Concurrently, Mn(III) MHAT catalyst **IX** can undergo transmetalation with a hydrosilane reagent (**X**) to afford Mn–H intermediate **XI**.[16] Ensuing MHAT between **XI** and olefin **XII** would furnish tertiary radical **XIII** and Mn(II) intermediate **XIV**. With reduced forms of the photocatalyst and MHAT catalyst now present in solution, we anticipated that mild exogenous oxidants could promote electron transfer events that regenerate both ground-state Ir(III) photocatalyst **III** and starting MHAT catalyst **IX**.[27] 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] affording the desired C(sp^3)–C(sp^3) cross-coupled product **XVII** while regenerating Ni catalyst **XV**.

Recognizing the importance of the "magic methyl effect" in pharmaceutical design,[28] we first evaluated our proposed olefin-alcohol coupling in the context of deoxygenative hydromethylation using alkene **1** and methanol as a widely available yet non-traditional methylating agent (**Table 1**). Delightfully, upon optimization, quaternary product **2** was obtained in 75% yield using Ir photocatalyst **I** under standardized 450 nm Integrated Photoreactor (IPR) irradiation.[29] In addition to these photocatalytic parameters, our optimal conditions featured the hydrosilane 1,1,3,3-tetramethyldisiloxane (TMDS), benzoyl peroxide as a mild oxidant, Mn(dpm)$_3$ for catalytic MHAT activation and a Ni-scorpionate catalyst (formed *in situ* from Ni(acac)$_2$ and trispyrazolylborate ligand KTp*)[23] for radical sorting. As outlined in **Table 1**, judicious catalyst selection proved essential for reactivity, an optimization requirement fa-

Table 1. Control Reactions and Optimization Conditions[a]



1 3 equiv **2**

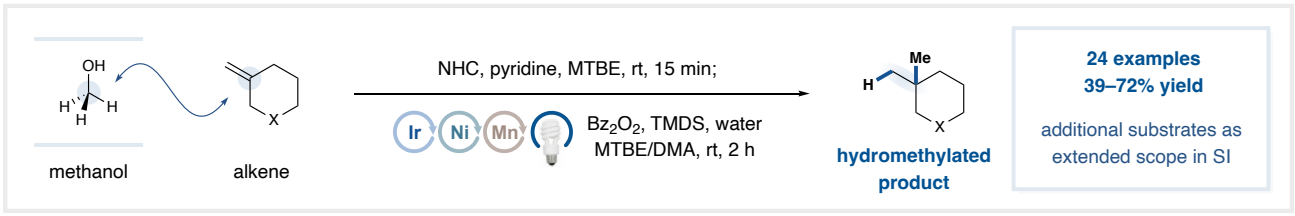
entry	deviation	yield[b]
1	none	75%
2	Fe(OEP)Cl instead of **4**	2%
3	no Ni catalyst	10%
4	Ni(acac)$_2$ instead of **4**	67%
5	Fe(acac)$_3$ instead of **3**	9%
6	Co(acac)$_2$ or Co(salen) instead of **3**	4%
7	no light	5%
8	no photocatalyst	19%
9	no TMDS	0%
10	no oxidant	0%
11	no Mn catalyst	0%

[a]Performed with alkene (0.05 mmol, 1.0 equiv), alcohol (3 equiv), NHC (3.3 equiv), pyridine (3.15 equiv). [b]Yields determined by NMR with 1,4-dinitrobenzene as internal standard. See Supporting Information for experimental details.

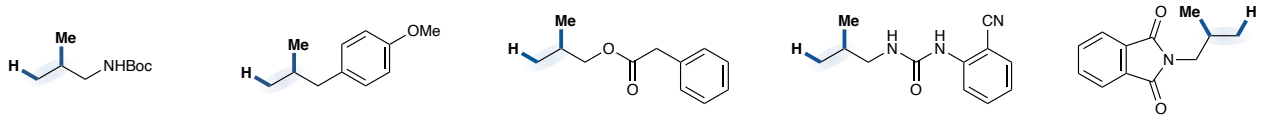
cilitated by the catalytic versatility of both MHAT and metallaphotoredox radical sorting activation modes.[3,16] For the radical sorting step, product **2** was obtained in minimal yield using conventional Fe-based catalysts or in the absence of a sorting catalyst. By contrast, diketone- and KTp*-ligated Ni complexes—which are known to promote radical sorting reactivity—were each effective in some capacity.[23,15] Moreover, Mn-catalyzed olefin activation emerged as a privileged option over Fe–H, Co–H, and MHAT-free systems.[16] When considering relative metal–carbon bond strengths, MHAT-relevant complexes based on Fe or Co are more thermodynamically suited to compete with Ni for methyl radical capture,[30] consistent with open-shell formation of Co–alkyl intermediates in previously reported MHAT systems.[31] Beyond differences in redox potentials, we hypothesize that the more weakly binding Mn catalyst avoids radical capture and off-cycle Mn–methyl formation, instead favoring productive Mn(III)–H activity.[16,30,31] These unique advantages of synergistic Ir/Ni/Mn triple catalysis for olefin activation and radical sorting are an emerging topic that will be addressed in subsequent studies by our laboratory. Lastly, additional control reactions indicated that blue light, photocatalyst, and hydrosilane were required for reactivity, confirming the operative nature of photoredox and MHAT activation steps within this protocol (see SI for details).

With optimal conditions in hand, we next evaluated the alkene scope for this transformation. To our delight, Markovnikov hydromethylation was achievable with full branched selectivity across a range of alkene substitution patterns (**Table 2**). Notably, while terminal olefins furnish less

Table 2. Scope of Metallaphotoredox Cross-Coupling of Alkenes and Methanol[a]

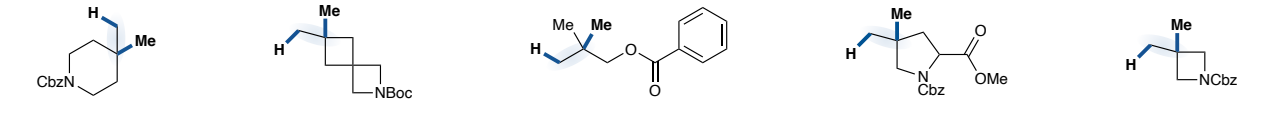


alkene scope

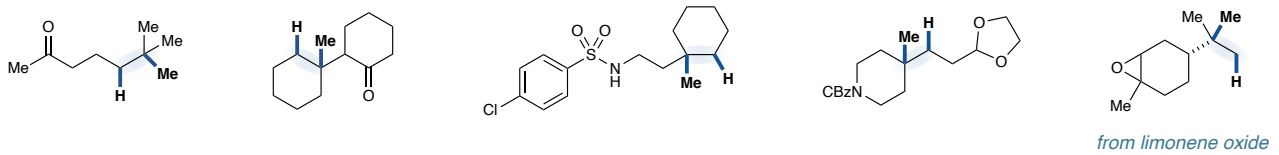


6, 56% yield | **7**, 63% yield | **8**, 39% yield[b] | **9**, 69% yield | **10**, 49% yield[b]

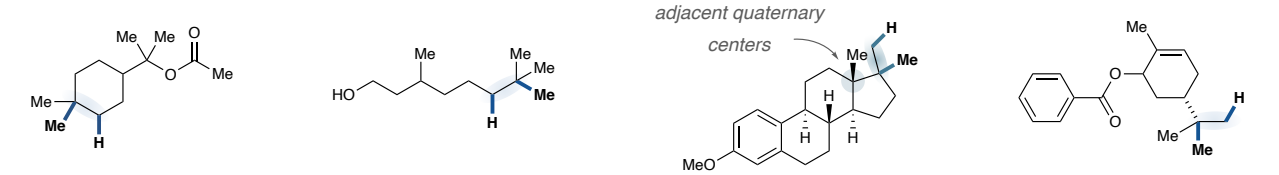
quaternary center



2, 72% yield | **11**, 59% yield | **12**, 50% yield | **13**, 54% yield | **14**, 51% yield



15, 59% yield[c] | **16**, 51% yield[b] | **17**, 58% yield | **18**, 43% yield | *from limonene oxide* **19**, 68% yield[b]



from terpinyl acetate **20**, 64% yield[b] | *from citronellol* **21**, 64% yield[c] | *from estrone core* **22**, 51% yield | *from carveol* **23**, 48% yield

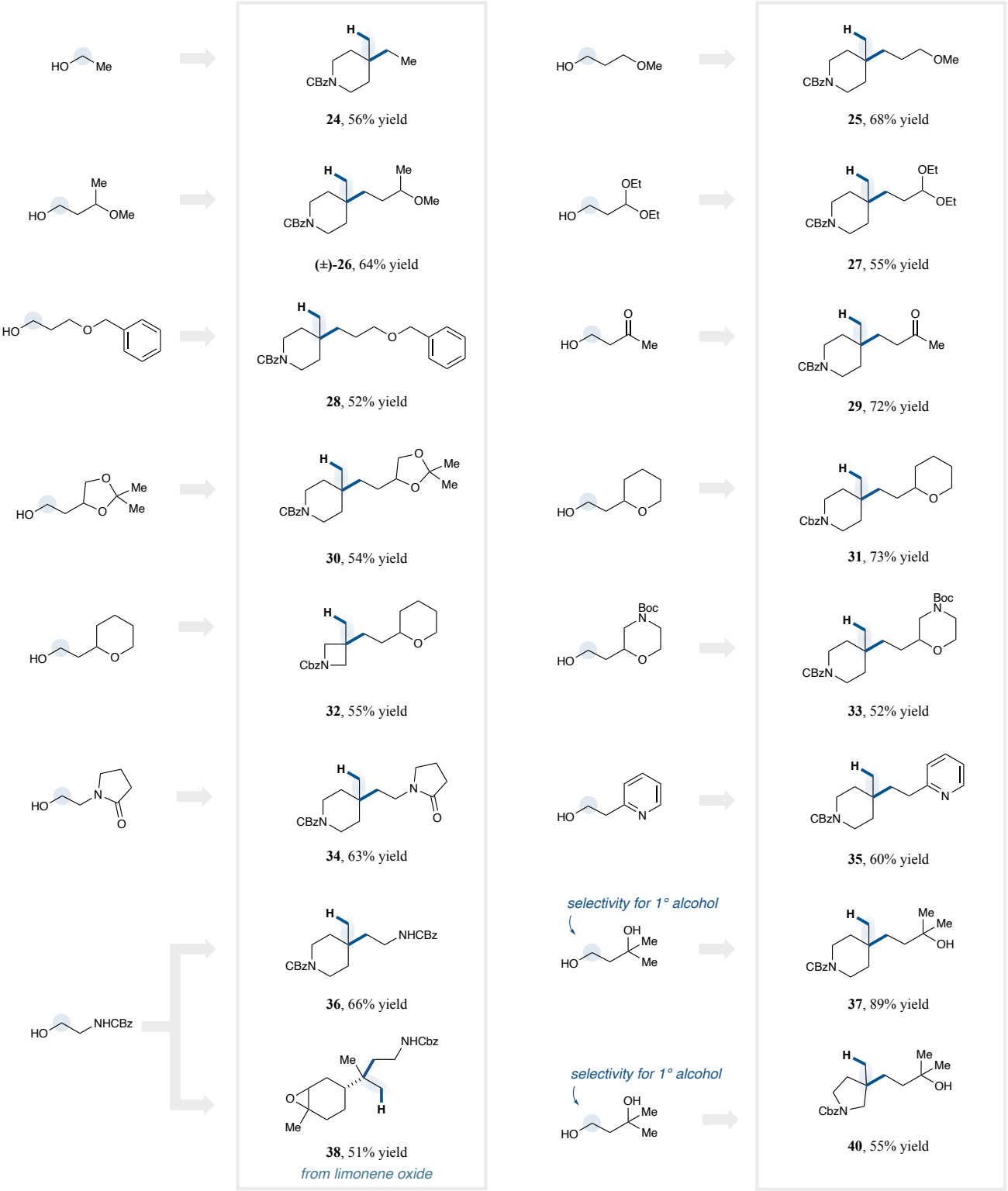
[a]Coupling performed with methanol (3 equiv), **NHC-1** (3.3 equiv), pyridine (3.15 equiv) in MTBE (0.50 M) for 15 min at room temperature, then manganese catalyst **3** (20 mol%), nickel catalyst **4** (10 mol%), iridium photocatalyst **5** (0.25 mol%), benzoyl peroxide (4 equiv), potassium acetate (0.5 equiv), water (5 equiv), alkene (0.5 mmol, 1 equiv), TMDS (5 equiv) and performed NHC adduct in DMA:MTBE (1:4, 0.067 M) with blue LED irradiation for 2 h at room temperature. [b]Yields determined by NMR with 1,4-dinitrobenzene as internal standard. [c]Yields determined by NMR with 1,4-dinitrobenzene as internal standard reference to the known products due to volatility. See Supporting Information for experimental details.

nucleophilic secondary radicals upon MHAT activation,[32] these intermediates consistently undergo facile radical sorting to efficiently deliver methylated products (**6**–**10**, 39–69% yield). Additionally, substrates bearing highly substituted di- or trisubstituted alkenes could be easily leveraged as tertiary radical precursors via MHAT. This extension resulted in products containing quaternary centers (**2** and **11**–**18**, 43–72% yield), valuable linkages that remain elusive under most typical cross-coupling conditions.[21,22] Given the absence of low-valent Ni intermediates in Ni(II)/Ni(III) radical sorting platforms,[23,15] a selection of functional groups typically sensitive to oxidative addition, including allylic carboxylates and aryl halides, are well-tolerated in these chemoselective examples.[33] Beyond these standard cases, a range of naturally-sourced terpene, terpenoid and hormone-derived substrates were competent within this protocol (**19**–**22**, 51–68% yield), furnishing elusive motifs such as adjacent quaternary centers in short order. By exploiting MHAT kinetic preferences for activating minimally substituted and less electron-rich π-systems,[34] we also observed that terminal cases are selectively functionalized over other substitution patterns (**23**, 48% yield), a finding that could inform protecting group-free, C(sp^3)-enriching coupling sequences of polyolefin feedstocks. Collectively, this protocol affords medicinally valuable gem-dimethyl, methylcycloalkyl and quaternary carbon units from olefins,[35] all while using a bulk solvent (i.e. methanol) as an atypical methylating reagent.

To probe the versatility of this new coupling technology, we next investigated the scope of alcohols amenable to

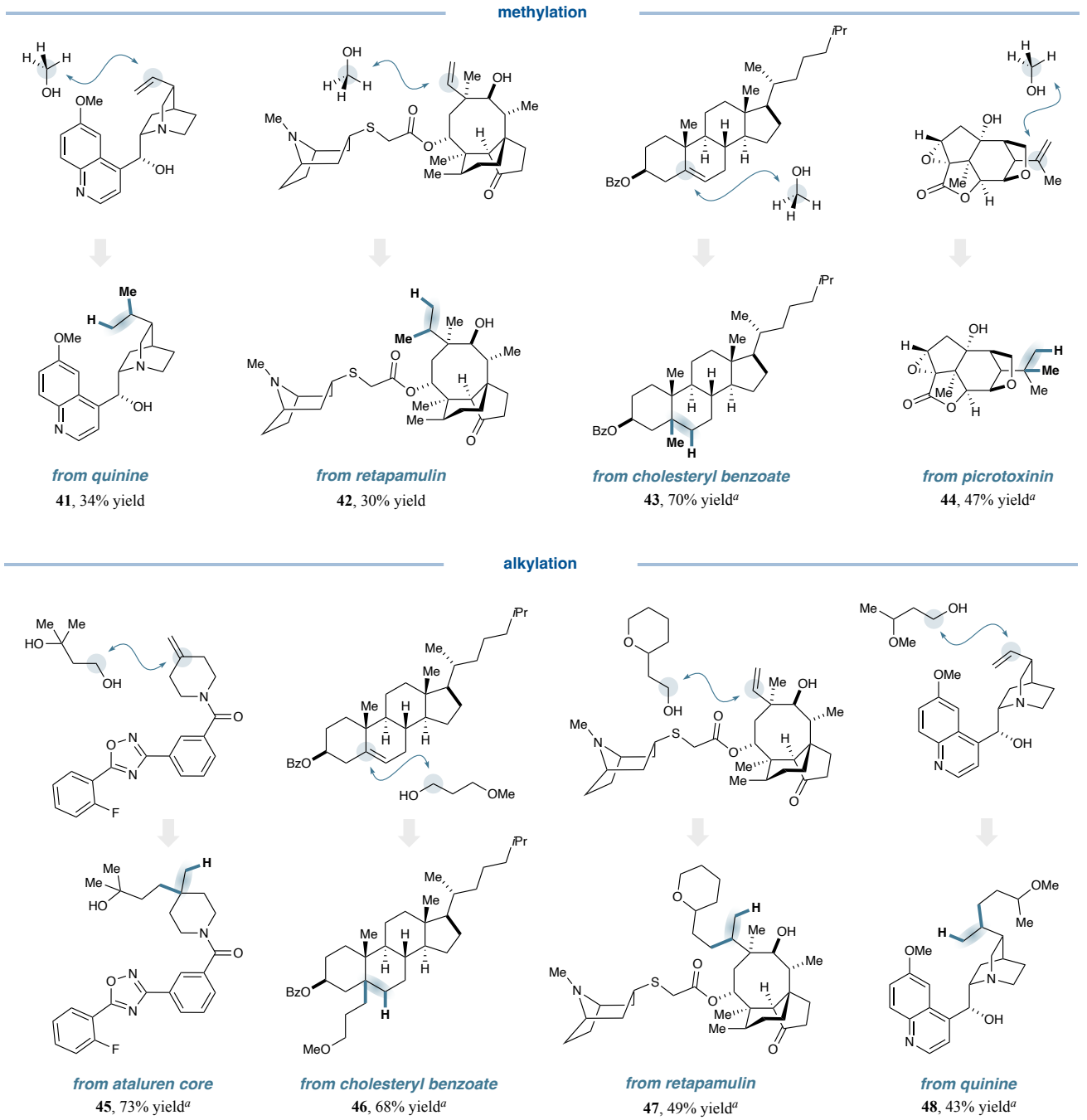
Table 3. Scope of Metallaphotoredox Cross-Coupling of Alkenes and Alcohols[a]

alcohol scope



[a]Coupling performed with alcohol (3 equiv), **NHC-1** (3.3 equiv), pyridine (3.15 equiv) in MTBE (0.50 M) for 15 min at room temperature, then manganese catalyst **3** (20 mol%), $Ni(acac)_2$ (10 mol%), iridium photocatalyst **5** (0.25 mol%), benzoyl peroxide (3 equiv), potassium acetate (0.5 equiv), water (5 equiv), alkene (0.5 mmol, 1 equiv), TMDS (5 equiv) and performed NHC adduct in DMA:MTBE (1:2, 0.11 M) with blue LED irradiation for 2 h at room temperature. See SI for experimental details. All yields are isolated.

Table 4. Deoxygenative Hydromethylation and Hydroalkylation of Complex Alkenes



[a]Yields determined by NMR with 1,4-dinitrobenzene as internal standard reference. See Supporting Information for experimental details.

deoxygenative hydroalkylation (**Table 3**). Using an alternative Ni-diketonate sorting catalyst,[15,23] an array of primary substrates were paired with tertiary olefin-derived radicals to efficiently access diverse quaternary products (see SI for additional examples of hydromethylation or hydroalkylation). In these cases, simple hydrocarbon-, ether- or acetal-containing alcohols were broadly successful (**24**–**30**, 52–68% yield), as were substrates bearing tetrahydropyran (**31** and **32**, 73% and 55% yield, respectively), morpholine (**33**, 52% yield), lactam (**34**, 63% yield) or pyridine (**35**, 60% yield) heterocyclic functionality. Moreover, the functional group tolerance of this method allowed for retention of protic motifs such as amine derivatives or unprotected distal alcohols (**36**–**40**, 51–89% yield). The latter finding is particularly significant when considering the selectivity of NHC-mediated deoxygenation for activating less-substituted sites within diol substrates.[15] As such, this protocol could enable the stepwise and site-selective elaboration of native polyols into complex scaffolds using olefin feedstock partners.

Lastly, to rapidly produce drug-like, C(sp^3)-rich molecular architecture from native functionality,[8] we harnessed olefin-alcohol coupling for the late-stage derivatization of medicinally-relevant scaffolds (**Figure 3**). Using methanol, hydromethylated products were expediently furnished from

bioactive compounds bearing a typically unreactive olefin within their structure, including the antimalarial quinine (**41**, 34% yield), the antibiotic retapamulin (**42**, 30% yield), common steroids (**43**, 70% yield) and the plant-derived stimulant picrotoxinin (**44**, 47% yield). Delightfully, this reactivity was also extendable to other quaternary carbon formations, as both the aforementioned substrates and a derivative of the muscular dystrophy therapeutic ataluren were efficiently hydroalkylated using diverse primary alcohols (**45**–**48**, 43–73% yield). Across all cases, the unique tolerance of this method for labile functionality (including readily-oxidized amines and sulfides, coordinating alcohols and pyridines, or oxidative addition-prone 1,2,4-oxadiazoles)[36,37] was critical for the generation of complex molecular architecture in an efficient manner.

Collectively, these examples underscore the utility, expediency, and selectivity offered by metallaphotoredox olefin-alcohol coupling when constructing aliphatic scaffolds of medicinal relevance. Moreover, we envision that synergistic Ir/Mn/Ni triple co-catalysis can be generically advantageous for C(sp^3)–C(sp^3) bond formations between olefins and other radical sorting partners. To facilitate such advances, further mechanistic evaluation and application of these photocatalytic modes is currently underway.

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Notes

D.W.C.M. declares a competing financial interest with respect to the Integrated Photoreactor.

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