JACS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
Cite This: *J. Am. Chem. Soc.* 2019, 141, 7709−7714
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Hydroalkylation of Olefins To Form Quaternary Carbons

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Supporting Information

ABSTRACT: Metal-hydride hydrogen atom transfer (MHAT) functionalizes alkenes with predictable branched (Markovnikov) selectivity. The breadth of these transformations has been confined to π-radical traps; no sp^3 electrophiles have been reported. Here we describe a Mn/Ni dual catalytic system that hydroalkylates unactivated olefins with unactivated alkyl halides, yielding aliphatic quaternary carbons.

Olefins represent versatile feedstocks and intermediates for chemical synthesis. Metal-hydride hydrogen atom transfer (MHAT) has emerged as a useful reaction platform for the branched-selective hydrofunctionalization of olefins. Its high chemoselectivity for olefins and mild reaction conditions have allowed its deployment in medicinal chemistry and natural product synthesis.[1] The bulk of these transformations involve carbon−heteroatom bond formation, whereas intermolecular C−C formation has been less explored and has largely required stoichiometric radical traps like π-electrophiles. Pioneering advances in the formation of C−C bonds are represented by hydrocyanations and hydrooximation from Carreira[2] and Boger.[3] More recently, Baran and co-workers developed a powerful variant of the Giese reaction[4,7d] as well as a creative protocol for hydromethylation (Figure 1A).[5] Finally, our group[6] and others[7] have investigated the branched-selective hydroarylation of olefins using MHAT, establishing olefins as progenitors of arylated quaternary centers.

The limited range of Markovnikov hydro-*alkylations* stems from a scarcity of alkyl radicalophiles. Whereas MHAT has relied historically on stoichiometric radical traps such as O_2,[1a] our group has become interested in combining MHAT with a second catalytic cycle, thereby expanding the variety of coupling partners.[1b] Recently, we established a dual catalytic platform to allow for the hydroarylation of unactivated olefins[6b,c] as well as the addition of carbanion surrogates to aldehydes,[8] yielding branched-selective products otherwise inaccessible by traditional radical reactions. A dual catalytic approach for the hydro*alkylation* of olefins could access known alkyl coupling partners (e.g., alkyl halides,[9] carboxylic acids[10]) in lieu of alkyl radical traps and cross a longstanding methodological gap.

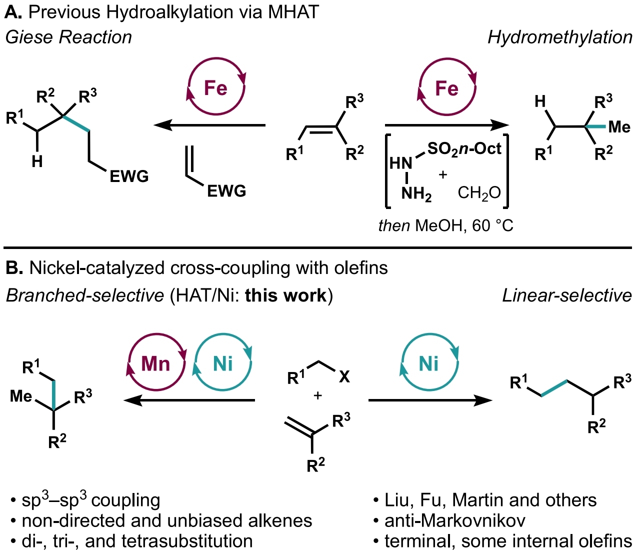

Figure 1. Prior hydroalkylation reactions using (a) MHAT and (b) Ni catalysis.

Markovnikov hydroalkylation would also provide a new transform to dissect quaternary carbons, which remain challenging motifs in natural products and drug scaffolds. While radical chemistry has emerged as a useful platform for the construction of sterically congested motifs,[11,12] sp^3-sp^3 cross-coupling remains an underdeveloped area for quaternary carbon formation.[9a,13] The use of nickel catalysis to generate and engage open-shell intermediates has been revolutionized by Fu,[9a,14] but its use in the construction of quaternary carbons has only recently been described,[6c,15,16] with the development of alkylation reactions restricted to stabilized radicals[17] or Giese reactions.[18] Recently, olefins have become viable coupling partners in reductive coupling[19] and nickel catalysis as surrogates for organometallic reagents.[17,20] Whereas these nickel hydride-mediated methods yield anti-Markovnikov (linear) hydrofunctionalized products, MHAT dual catalysis provides access to branched products, even quaternary carbons, using similarly benign starting materials and conditions (Figure 1B). Herein we describe an approach for the hydro*alkylation* of unactivated olefins using Mn/Ni dual catalysis.

Our previous method to form arylated quaternary centers[6c] led us to hypothesize that our reaction design might translate to alkylation. Namely, an MHAT-generated tertiary radical or organometallic could be intercepted by a low valent nickel species, which could subsequently engage with an alkyl halide (or alkylnickel species) and yield our desired product upon reductive elimination (Figure 2A).[10b,21] Regeneration of low

Received: March 14, 2019
Published: April 29, 2019

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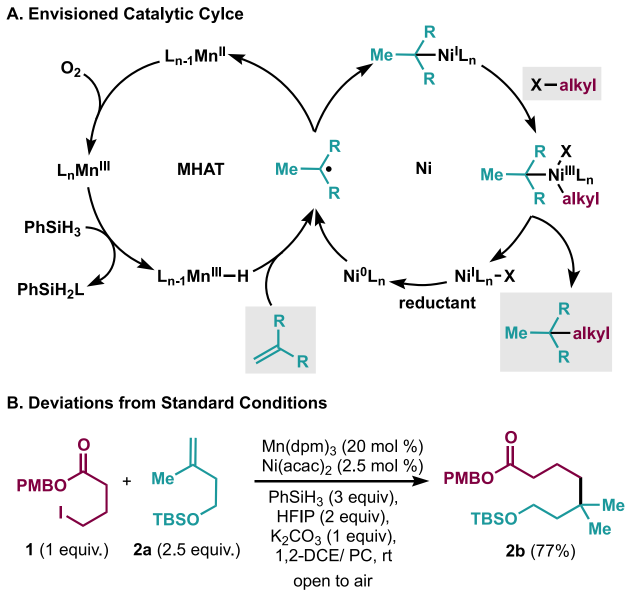
DOI: 10.1021/jacs.9b02844

valent nickel may proceed through formation of Ni–H via silane or Mn–H.


A. Envisioned Catalytic Cycle

B. Deviations from Standard Conditions

Entry	Deviations from Above	Yield %[a]
1	none	77 (72)[b]
2	$Fe(dpm)_3$ instead of $Mn(dpm)_3$	0 (20)[c]
3	no $Mn(dpm)_3$	none
4	no $Ni(acac)_2$	20 (trace)[d]
5	no K_2CO_3	55
6	no HFIP	36
7	no propylene carbonate (PC)	55
8	*i*PrOH instead of HFIP	54
9	Ph(*i*-PrO)SiH_2 instead of $PhSiH_3$	50 (27)[c]

Figure 2. (a) Plausible catalytic cycle for the hydroalkylation of olefins. (b) Optimization parameters. [a] 0.1 mmol scale, yield determined by GC-FID using 1,3,5-trimethoxybenzene as an internal standard. [b] 0.3 mmol scale, isolated yield 15:1 branched (*b*): linear (*l*) product. [c] No HFIP. [d] Using 2-iodoethyl benzoate instead of **1**. dpm = dipivaloylmethane; HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol; 1,2-DCE = 1,2-dichloroethane; PC = propylene carbonate.

A successful Markovnikov olefin coupling would require an override of the inherent anti-Markovnikov migratory insertion found in Liu[20a] and Fu's[17] Ni–H systems. Unfortunately, initial attempts to utilize our Fe/Ni system[6c] that provides such override yielded only trace product (Figure 2B). A polar solvent screen, however, indicated propylene carbonate (PC)[22] was superior to *N*-methylpyrrolidinone (NMP). Curiously, PC as a cosolvent obviated the need for Mn^0 and MnO_2 coreactants, which we had proposed to turn over the catalytic cycles. Instead the reaction could be run open to air.[23]

Alkyl iodides coupled efficiently, whereas alkyl bromides, redox active esters, and sulfones yielded trace or no product (see Supporting Information (SI)). A screen of MHAT catalysts indicated that $Mn(dpm)_3$[24] outperformed $Fe(dpm)_3$ and $Co(dpm)_2$. We did observe some product formation in the absence of Ni, but this background reactivity did not prove general and the yield could not be improved without the Ni cocatalyst. Similar to our arylation chemistry, traditional mono-, di-, and tridentate ligands on Ni either provided no improvement in yield or ablated reactivity. Preparatively useful yields were finally obtained with alcoholic additives: isopropanol led to marginal improvement, and HFIP was found to almost double the yield. Due to decreased efficiency observed with Ph(*i*PrO)SiH_2, it is unlikely that the improved yield is due to an alcohol–silane complex. However, a noticeable color change from black to rust-red occurs when HFIP/K_2CO_3 is added to $Mn(dpm)_3$ in the absence of silane. Attempts to isolate and characterize this complex were unsuccessful. We cannot rule out the formation of a dimeric species bridged by the alcohol additive.[7d,25]

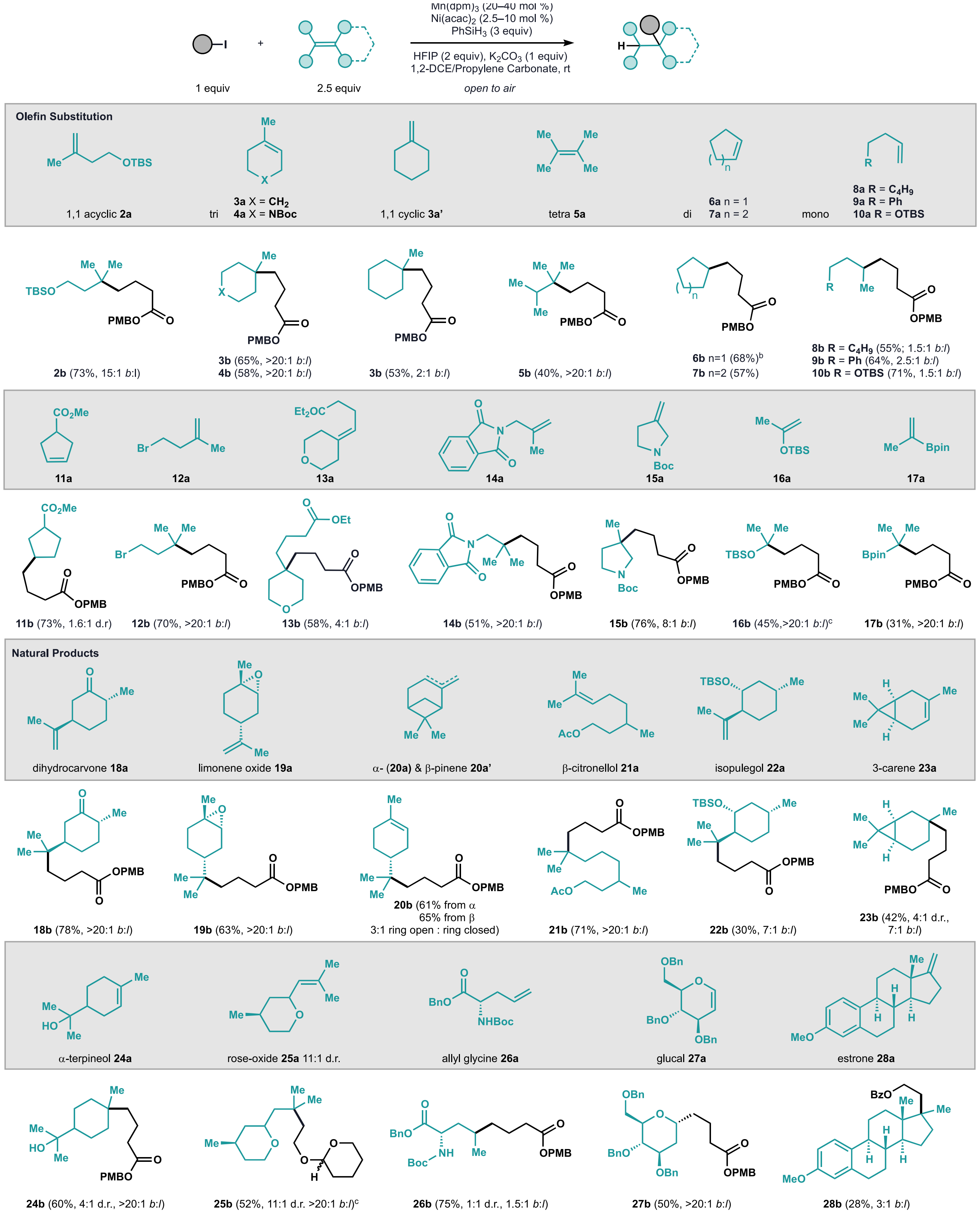
With optimized conditions in hand we began to investigate the breadth of olefin compatibility (Table 1, **2–28**). The *para*-methoxybenzyl ester of 4-iodobutyric acid (**1**) allowed the clear identification of products by both UV/vis and mass spectrometry.[26] While our interest was on the formation of quaternary centers, we were pleased to find that all variants of olefin substitution were well-tolerated (**2–10**) and even tetrasusbtituted olefins coupled, albeit in diminished yield. Overall, the transformation exhibited exquisite regiocontrol with tri- and tetrasubstituted olefins yielding products with high branched-to-linear ratios (*b*:*l*), highlighting the selectivity of this method. Whereas trisubstituted olefins generally afforded higher regioselectivity than their exocyclic counterparts (**3a** vs **3a′**), five-membered rings with exocyclic alkenes retained high branched selectivity (**15**), potentially a result of increased rate of MHAT due to strain release. Interestingly, terminal olefins (**8–10**) were subject to a background linear reaction, a trend also noted by Carreira with $Mn(dpm)_3$-mediated transformations.[27] Three hypotheses may explain this aberrant selectivity: a background Ni-only mediated pathway, analogous to reactivity observed by Liu,[20a] lowered regioselectivity of MHAT itself due to similar transition state energies of developing C-centered radicals, or a competitive hydrometalation pathway mediated by low valent manganese.[28]

The reaction displayed high functional group compatibility in its tolerance of esters (**11**, **13**, **21**, **26**), phthalimides (**14**), carbamates (**4**, **15**, **26**), silyl enol ethers (**16**), boronic esters (**17**), and epoxides (**19**). Interestingly, the reaction with alkenes proceeded with high chemoselectivity even in the presence of a primary alkyl bromide (**12**), which did not engage in the reaction or undergo protodehalogenation. Although primary (**21**) and secondary alcohols (**22**) required protection due to competitive silylation, tertiary alcohols did not affect catalysis (**24**). Heteroatom substitution[29] on or adjacent to the alkene was well tolerated (**16**, **17**, **25**), but, in general, remotely functionalized alkenes returned the highest yields (e.g., **21**) and proximal branching lowered efficiency (**22**, **28**).

The abundance and diversity of olefins from commercial sources allowed a rapid survey of alkene scope. We were pleased to observe that a variety of natural product scaffolds (**18–28**) could be cleanly alkylated. A range of simple to complex terpenoids were successfully employed, which constitutes a new utilization of the chiral pool and potential access to new flavors and fragrances. The transformation of terpenes, whose hallmark features often are electronically unbiased,[30] hindered alkenes, have benefited immensely from MHAT methodology[1,4,6,7d,29] and served as particularly efficient scaffolds for this methodology. Notably, limonene oxide (**19a**) and 3-carene (**23a**) were both hydroalkylated with their scaffolds intact: no retrocyclization of the epoxide or

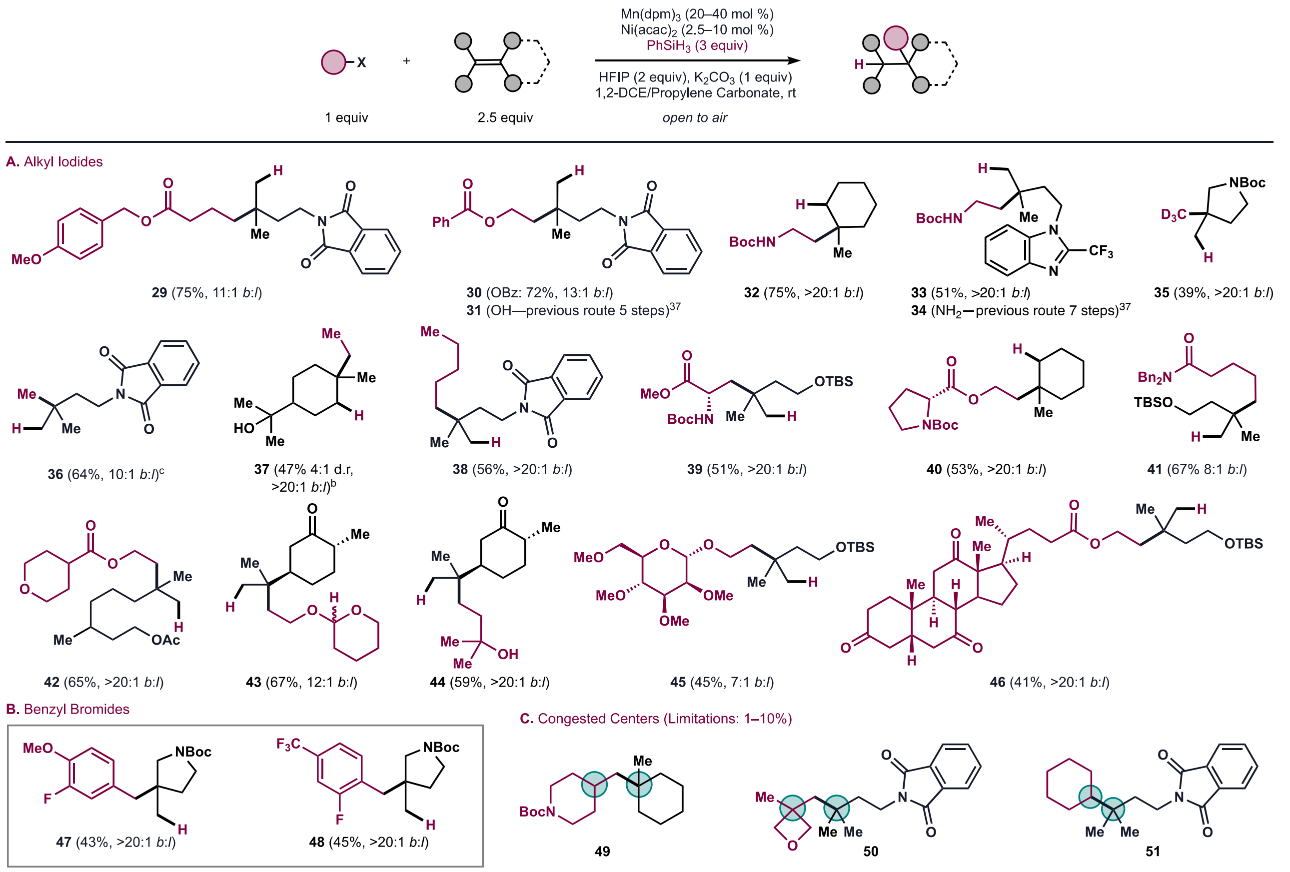
DOI: 10.1021/jacs.9b02844
J. Am. Chem. Soc. 2019, 141, 7709–7714

Table 1. Hydroalkylation Olefin Scope[a]



[a] 0.3 mmol scale, isolated yield; see SI for specific catalyst loading. *b:l* = branched/linear ratio. [b] Reaction run under an air balloon. [c] 5 equiv of olefin added in two portions (2.5 equiv at start and 2.5 equiv at 24 h).

Table 2. Alkyl Halide Scope[a]



[a]0.3 mmol scale, isolated yield; see SI for specific catalyst loading. *b:l* = branched/linear ratio. [b]0.1 mmol scale. [c]Isolated as a mixture with hydrogenation, yield determined by NMR. Further purified by prep HPLC.

cyclopropane motifs was observed. Pinene (**20**), on the other hand, predominantly underwent ring opening (3:1 ring opened/closed ratio) and yielded an alkylated limonene derivative (**20b**), which did not undergo further hydrogenation of the resulting trisubstituted olefin.[31] In some cases, alkylation noticeably altered the odor of these scaffolds, as was the case with rose oxide (**25**), which underwent alkylation with high branched selectivity. Substrates that contained existing stereocenters exhibited modest stereoselectivity, as was the case with terpineol (**24b**) and carene (**23b**).

This method allowed the union of diverse metabolic building blocks (terpenes, amino acids, sugars) by strong covalent bonds. In addition to terpenes, ketide-like fragments corresponding to oxygen-polarized carbon chains could be appended. This merger complements Giese reactivity, which yields β-substitution, whereas **24** and **25** correspond to γ- and α-connections relative to a latent carbonyl. Allylglycine (**26**) proved to be a poor substrate (amino acids could be incorporated efficiently in Table 2; see above), but glucals coupled efficiently and yielded the C-glycoside product (**27**) as a single diastereomer.[32,33] Furthermore, a single diastereomer of estrone derivative **28b** was observed, remarkably forming vicinal quaternary centers, albeit in reduced yield.

A diverse range of alkyl halides successfully coupled to form quaternary carbon centers (Table 2, **29**−**48**). Sensitive functional groups such as acetals (**43**) and nitrogen containing heterocycles (**33**) were unaffected by the coupling. Numerous simple alkyl chains could be appended to affect hydromethylation, ethylation, and pentylation reactions with similar efficiency. Ethylation of terpineol (**37**) resulted in a marked change in fragrance: from the sharp pine parent compound odor to a less-pungent musty, citrus. Methyl-d_3 iodide was also compatible, providing the isotopically mixed geminal dimethylpyrrolidine **35**. More complex alkyl iodides also proceeded in good yield, allowing for one-step installation of sugar- and steroid-bearing motifs **45** and **46**. Prenyl groups—common motifs in natural products could also be appended using this method. While prenyl bromide displayed poor reactivity due to competitive MHAT, we were pleased to find that a prenyl surrogate, 4-iodo-2-methylbutan-2-ol, yielded unnatural terpene **44** with excellent selectivity.

MHAT dual catalysis provides an orthogonal approach to phthalimide-containing compounds **30** and **36**.[34] Phthalimide **36** has previously been accessed through disconnection at the quaternary center using a Cu-nanoparticle catalyzed Kumada coupling with the *tert*-alkyl Grignard.[35,36] Phthalimide **31**, previously accessed in five steps from dimedone, has been described in the patent literature in the development of drugs for the treatment of inflammatory disorder and microbial disease.[37] Conversely, our method allows direct access to the quaternary center, yielding **30** in two steps after deprotection.

Stereochemistry on the alkyl iodide was found to translate well to the products, with no epimerization observed in the case of the iodoalanine (**39**), proline (**40**), or sugar substrates (**45**). Importantly, the use of iodoalanine provides enantiomerically pure access to unnatural amino acid **39**, providing an orthogonal approach to the racemic conjugate addition product from dehydroalanine.

Whereas benzyl iodides were poorly tolerated under the reaction conditions, we were pleased to find that benzyl bromides coupled in moderate yield (**47**, **48**). Furthermore, benzyl electrophiles provide an intriguing disconnection. An sp^2—sp^3 bond scission would transform the product to an arene and neopentyl cross-coupling partner, which retains structural complexity and oftentimes requires an organometallic reagent. Consequently, similar scaffolds have been accessed by formation of a mixed ketone, alkylation, and Wolff—Kishner deoxygenation—overall a seven-step sequence.[38] Disconnection to the benzyl electrophile and alkene allows scission of the quaternary carbon in a logical and simplifying transform.

While this method makes significant progress in the formation of sterically congested aliphatic centers, the transformation is sensitive to the steric environment on the alkyl halide. α-Branching (**49**), neopentyl (**50**), and secondary alkyl iodides (**51**) were found to proceed in low yield, predominantly lost to competitive protodehalogenation. This could imply that oxidative addition or a more sterically congested Ni center impedes productive reductive elimination.

In summary, we have reported a Markovnikov-selective hydroalkylation of unbiased olefins[30] using diverse alkyl iodides and benzyl bromides. The combination of Mn-mediated MHAT catalysis[39] and Ni catalysis enable an unprecedented synthesis of quaternary carbons. The mild reaction conditions and robust functional group compatibility support its utility for late stage modification of small molecules. Efforts are underway to expand this chemistry to more sterically congested centers and complex natural products.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b02844.

Materials and methods; details related to synthesis and experiments; X-ray data (PDF)

NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support was provided by the National Science Foundation (GRFP to S.A.G.) and the National Institute of Health (R35 GM122606), as well as a generous Scientific Advancement grant from Boehringer-Ingelheim. We thank Dr. Jason S. Chen and Brittany Sanchez for help with separations and analysis.

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(31) Using (−)-limonene as the olefin gave a complex mixture of products with reactivity observed at both olefins. Overall, compounds containing multiple olefins did not provide selectivity. For other examples, see SI.

(32) The protecting group on the glucal was found to be important for high regioselectivity. The use of acetate in place of benzyl resulted in a mixture of regioisomers (C2 vs C3 alkylation), resulting from an acetate-directed Ni-catalyzed alkylation at C3. A similar directing effect was observed using esters in ref 17.

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