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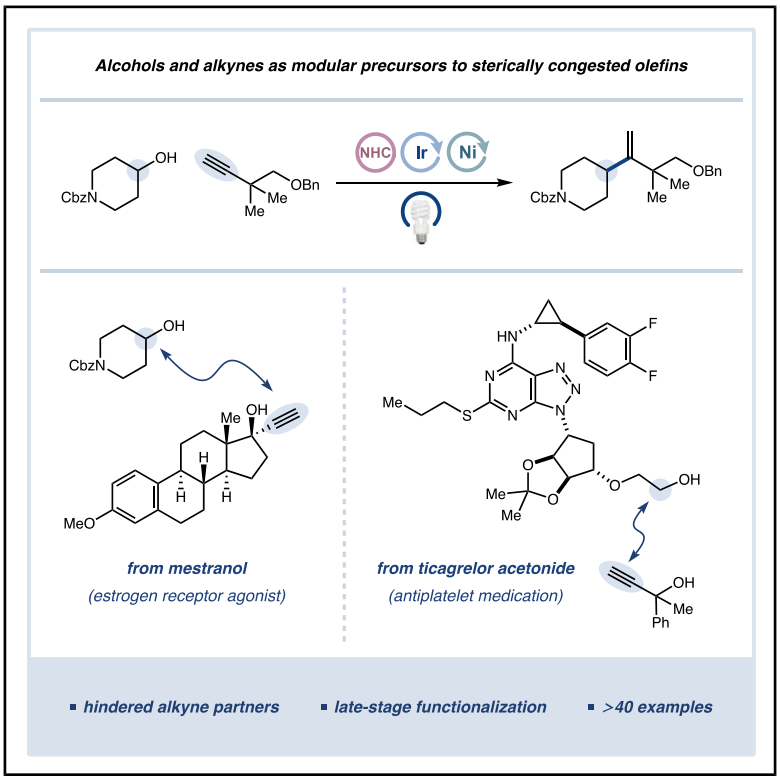
Carbometallation with alcohols: A facile strategy for olefin synthesis via deoxygenative hydroalkylation

Graphical abstract



Highlights

- Mild metallaphotoredox conditions furnish 1,1-di- and trisubstituted olefins
- Broad alcohol and alkyne scope with excellent functional-group tolerance
- Sterically congested products forged from rarely exploited α-tertiary alkynes
- Sequential hydroalkylation streamlines access to quaternary carbon centers

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In brief

Olefins are valuable intermediates for the construction of C(sp^3)-rich frameworks. 1,1-Disubstituted olefins are especially privileged precursors because their unique geminal substitution pattern enables diverse, regioselective transformations. Despite this utility, 1,1-disubstituted olefins are less readily available than other olefin substitution classes, and many established syntheses require harsh conditions or specialized starting materials. The reported mild metallaphotoredox hydroalkylation couples abundant alcohols with bench-stable alkynes to access 1,1-di- and trisubstituted olefins.

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Carbometallation with alcohols: A facile strategy for olefin synthesis via deoxygenative hydroalkylation

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THE BIGGER PICTURE Metallaphotoredox catalysis provides a mild platform for converting abundant, bench-stable chemical feedstocks into valuable synthetic intermediates. Olefins represent a desirable product class, as their selective functionalization can provide entry into medicinally relevant C(sp^3)-rich frameworks. Among these, 1,1-disubstituted olefins are prized for their distinctive regioselective reactivity yet remain comparatively underrepresented commercially, as established synthetic routes often require forcing conditions or specialized precursors. We report a modular metallaphotoredox hydroalkylation that unites abundant alcohols with bench-stable alkynes to furnish 1,1-di- and trisubstituted olefins. This reaction combines a broad alcohol and alkyne scope, including sterically encumbered α-tertiary alkynes, with excellent functional-group tolerance, enabling late-stage modification of complex molecules. A second hydroalkylation further transforms these olefin products into densely substituted C(sp^3)-rich molecules bearing quaternary carbon centers. This methodology expands access to sterically congested olefins, which we envision as useful building blocks for exploring complex molecular architectures in medicinal chemistry.

SUMMARY

Olefins are versatile intermediates in synthetic chemistry that can be readily transformed into valuable C(sp^3)-rich molecular structures. Efficient strategies for the modular assembly of olefins from abundant alkyl feedstocks are therefore highly desirable. Metallaphotoredox hydroalkylation provides an attractive approach to substituted olefins via coupling of readily accessible alkynes with bench-stable alkyl radical partners. While prior variants have employed radical precursors such as halides or carboxylic acids, alcohols—among the most abundant and structurally diverse alkyl feedstocks—remain underexplored. Herein, we disclose a metallaphotoredox deoxygenative hydroalkylation of alkynes to furnish olefins under mild conditions. The method exhibits a broad alcohol and alkyne scope with excellent functional-group tolerance. Notably, rarely exploited α-tertiary alkyne partners can be leveraged to furnish hindered 1,1-disubstituted olefins. The resulting olefins can undergo a second Markovnikov-selective hydroalkylation to generate quaternary carbon centers, highlighting the utility of alkynes as precursors to densely substituted aliphatic frameworks.

INTRODUCTION

The development of efficient cross-coupling methodologies remains a central objective in synthetic chemistry.[1] Among numerous advances made in this area, metallaphotoredox has emerged as a uniquely powerful catalytic platform, merging single-electron activation with mild transition-metal-mediated bond formation.[2] By harnessing abundant feedstock chemicals—such as amines, carboxylic acids, and C–H bonds—as radical precursors, metallaphotoredox enables cross-coupling strategies that are inaccessible through traditional two-electron pathways.[3–7] These methodologies are particularly well suited for constructing C(sp^3)-rich frameworks, which are increasingly recognized as core components of clinically successful small-molecule drug candidates.[8] Accordingly, the continued development of metallaphotoredox methods that streamline access to diversifiable intermediates for the synthesis of C(sp^3)-rich molecules remains an important goal.[9,10]

In this context, olefins represent valuable intermediates, particularly as precursors to C(sp^3)-rich structures.[11] Notably, acyclic olefins—accessible across the full range of alkene substitution patterns—provide modular entry points for aliphatic molecules via functionalization at either carbon atom (Scheme 1A). Among these substitution classes, 1,1-disubstituted olefins are especially

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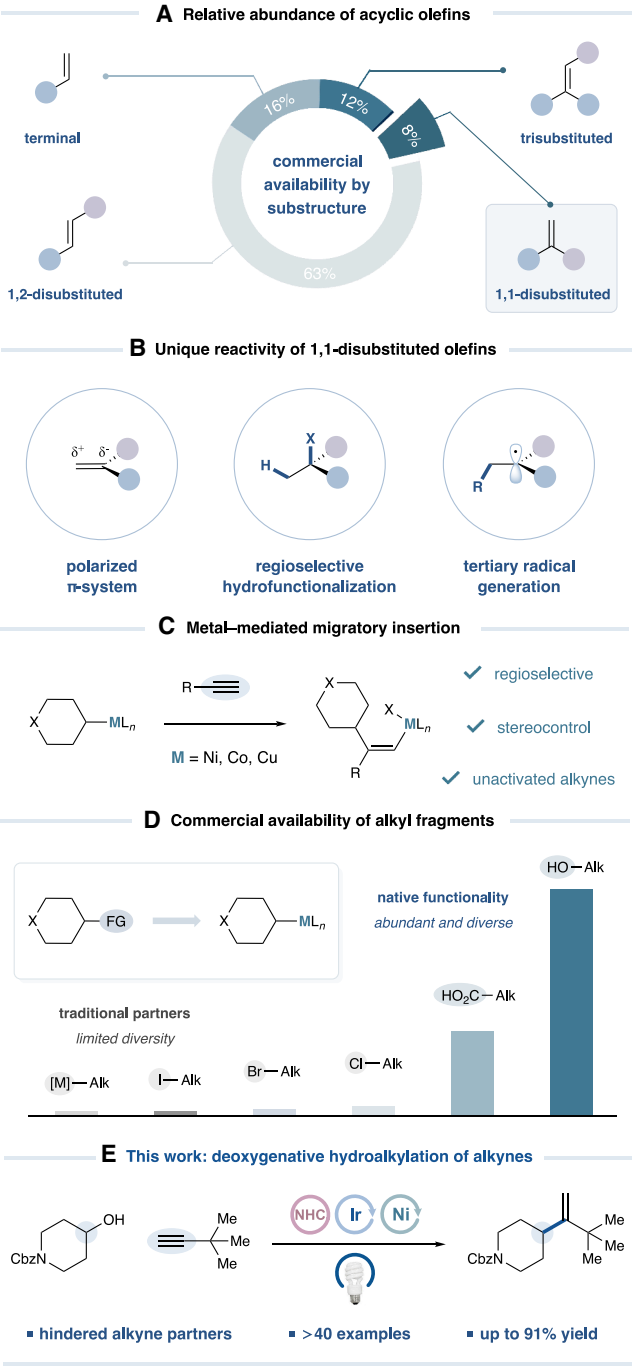

Scheme 1. Deoxygenative hydroalkylation of alkynes

coveted due to their unique synthetic versatility. This reactivity arises from the geminal alkyl substitution pattern, which increases electron density at the substituted carbon while enhancing electrophilicity at the unsubstituted terminal carbon (Scheme 1B). This intrinsic electronic bias has been leveraged in classical two-electron reactions to achieve regioselective transformations such as hydroamination,[12,13] hydroboration,[14,15] and hydrohalogenation,[16,17] as well as open-shell synthesis triggered by metal-hydride hydrogen atom transfer (MHAT)[18,19] or radical π-addition pathways.[20,21] Despite their synthetic utility, 1,1-disubstituted acyclic olefins remain commercially underrepresented, whereas 1,2-disubstituted variants are by far the most prevalent among typical vendors (Scheme 1A).[22]

Metal-mediated migratory insertion of alkynes into metal-alkyl bonds provides a powerful strategy for constructing 1,1-disubstituted olefins (Scheme 1C).[23–25] Beyond alkyne insertion into nickel-alkyl bonds,[24] other metal-catalyzed hydroalkylation strategies include iron-catalyzed *Z*-selective olefin synthesis,[26] copper-hydride insertion into terminal alkynes for *E*-selective olefin synthesis,[27] and ligand-controlled regiodivergent cobalt-hydride insertion into alkynes for *E*-1,2- or 1,1-disubstituted olefin synthesis.[25] Traditional methods for accessing these motifs—such as Tebbe[28] and Wittig[29,30] olefinations or metal-vinyl cross-couplings[31]—require harsh conditions or specialized precursors. By contrast, alkyne insertions proceed under mild conditions and exhibit high regioselectivity and stereoselectivity while employing an alkyne handle that is accessible, diverse, and bench-stable.[23] Crucially, achieving robust access to these motifs through metal-alkyl insertion requires an alkyl partner that is similarly abundant, mildly activated, and practical. Whereas traditional two-electron approaches to alkyne hydroalkylation require bespoke organometallic or iodide partners, the open-shell pathways of metallaphotoredox have enabled a broader range of alkyl sources to participate, including carboxylic acids,[32–34] C(sp^3)–H bonds,[35] benzyl chlorides,[36] and others.[37,38] Despite these advances, alcohols—arguably the most abundant and structurally diverse class of alkyl building blocks—have yet to be incorporated into alkyne hydroalkylation systems (Scheme 1D).[39] Given the recent progress in activating alcohols through NHC-mediated radical generation in our laboratory and others,[40–45] we sought to merge these manifolds to expand the chemical space accessible via alkyne hydroalkylation. Herein, we disclose a deoxygenative hydroalkylation of alkynes using alcohols as alkyl radical precursors to access 1,1-disubstituted olefins (Scheme 1E).

RESULTS AND DISCUSSION

Reaction development

We evaluated the proposed alkyne–alcohol coupling using secondary alkyl alcohol **1** and heptyne **2** (Figure 1; see section 10 in the supplemental information for details). Upon optimization, we were delighted to obtain the 1,1-disubstituted olefin product **3** in 85% yield with excellent regioselectivity (>20:1 r.r.) under 450 nm irradiation in an integrated photoreactor (IPR) (entry 1; see Figure S1 for standard assembly and Figures S33 and S34 in the supplemental information for product stability details). Our optimal conditions employed Ir[4,4′-di(*t*-Bu)ppy]$_2$(bpy)PF$_6$ as the photocatalyst, NiCl$_2$(glyme) as the nickel precatalyst, and ligand **5** (see Figures S2–S18 in section 4 of the supplemental information for further optimization details and Figures S19–S22 in section 5 of the supplemental information for photocatalyst **4** characterization data). Control experiments revealed that blue light, photocatalyst, nickel, and ligand are all critical for bond formation (entries 2–5), in line with the proposed mechanism outlined in Scheme 2. Alternative bipyridine ligands retain reactivity, albeit with a slightly diminished yield (entry 6). The

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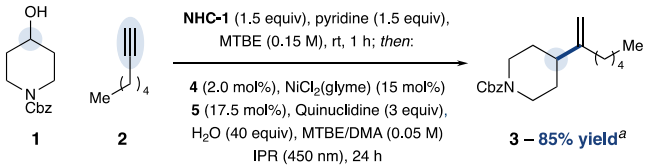
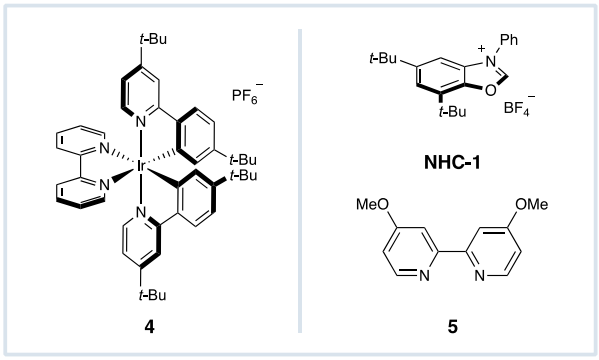




entry	deviation	yield[a]
1	none	85%
2	no light	0%
3	no photocatalyst **4**	0%
4	no $NiCl_2$(glyme)	0%
5	no ligand **5**	0%
6	4,4'-bis(t-Bu)-2,2'-bipyridine instead of **5**	66%
7	no quinuclidine	21%
8	no H_2O	41%
9	5 mol% $NiCl_2$(glyme), 5.8 mol% **5**	81%
10	4CzIPN instead of **4**	68%
11	no degassing with N_2	70%

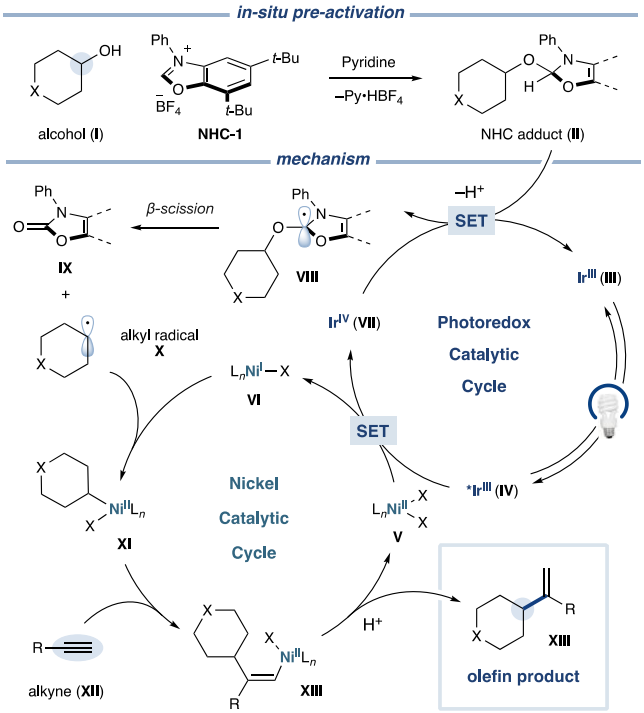
Figure 1. Optimization and control reactions

Reactions typically performed with 1.65 equiv 1, 1.0 equiv 2, and 1:1 MTBE/DMA. See the supplemental information for experimental details. aYield determined by 1H NMR. 4-CzIPN, 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene; Cbz, benzyloxycarbonyl; DMA, N,N-dimethylacetamide; glyme, 1,2-dimethoxyethane; MTBE, methyl tert-butyl ether; quinuclidine, 1-azabicyclooctane.

addition of base and water significantly enhances reactivity (entries 7 and 8), consistent with more efficient proton transfer during both the deprotonation of the oxidized NHC adduct and the protodemetallation of the Ni–vinyl complex **XII**, which is supported by deuterium-labeling studies (see Figure S32 in section 7 of the supplemental information for more details).[32,40,46] While 15 mol % nickel loading consistently gave the highest yields, 5 mol % nickel loading is also competent, exhibiting only minimal reduction in product formation (entry 9). Optimal reactivity is observed with photocatalyst **4** under an inert atmosphere, although organic photocatalysts and ambient oxygen are also tolerated (entries 10 and 11).

Mechanistic proposal

Although it has been well established that NHC-alcohol adducts promote reductive quenching of Ir(III) excited states,[40] Stern-



Scheme 2. Plausible mechanism for deoxygenative hydroalkylation of alkynes

Volmer experiments revealed that the nickel catalyst was the most competent fluorescence quencher for photocatalyst **4** (see Figures S23 and S24 in section 5 of the supplemental information for experimental details). Therefore, we propose an alternative mechanism in which the nickel catalyst engages in oxidative quenching of the excited-state photocatalyst and the resulting Ir(IV) species oxidizes the NHC-alcohol adduct. Scheme 2 outlines this plausible mechanism for the deoxygenative hydroalkylation of alkynes. Prior to irradiation, an alkyl alcohol (I) reacts with a benzoxazolium salt (**NHC-1**) to form the activated NHC-alcohol adduct II.[40] Upon visible light irradiation, the Ir(III) photocatalyst (III) undergoes excitation and intersystem crossing to generate the long-lived triplet excited state, *Ir(III) (**IV**).[47] Subsequent single-electron transfer (SET) from *Ir(III) (**IV**) to Ni(II) species **V** yields the reduced Ni(I) complex (**VI**) and the ground-state Ir(IV) photocatalyst (**VII**).[48] Adduct **II** can then undergo oxidation via SET from the ground-state Ir(IV) **VII** to regenerate Ir(III) photocatalyst **III** and, following deprotonation, carbon-centered radical **VIII**. This radical undergoes facile β-scission to produce an inert carbamate by-product (**IX**), as well as the desired alkyl radical **X**, which is supported by TEMPO trapping studies (see Figures S25–S31 in section 6 of the supplemental information for more details). This open-shell intermediate readily engages in oxidative radical capture with a low-valent nickel complex **VI** to generate the corresponding Ni(II)–alkyl species **XI**. Following association with alkyne **XII**, complex **XI** undergoes migratory insertion to forge a new carbon–carbon bond and generate the nickel–vinyl complex **XIII**. Based on our previous reports and the established mechanistic preference for *cis*-carbometallation,

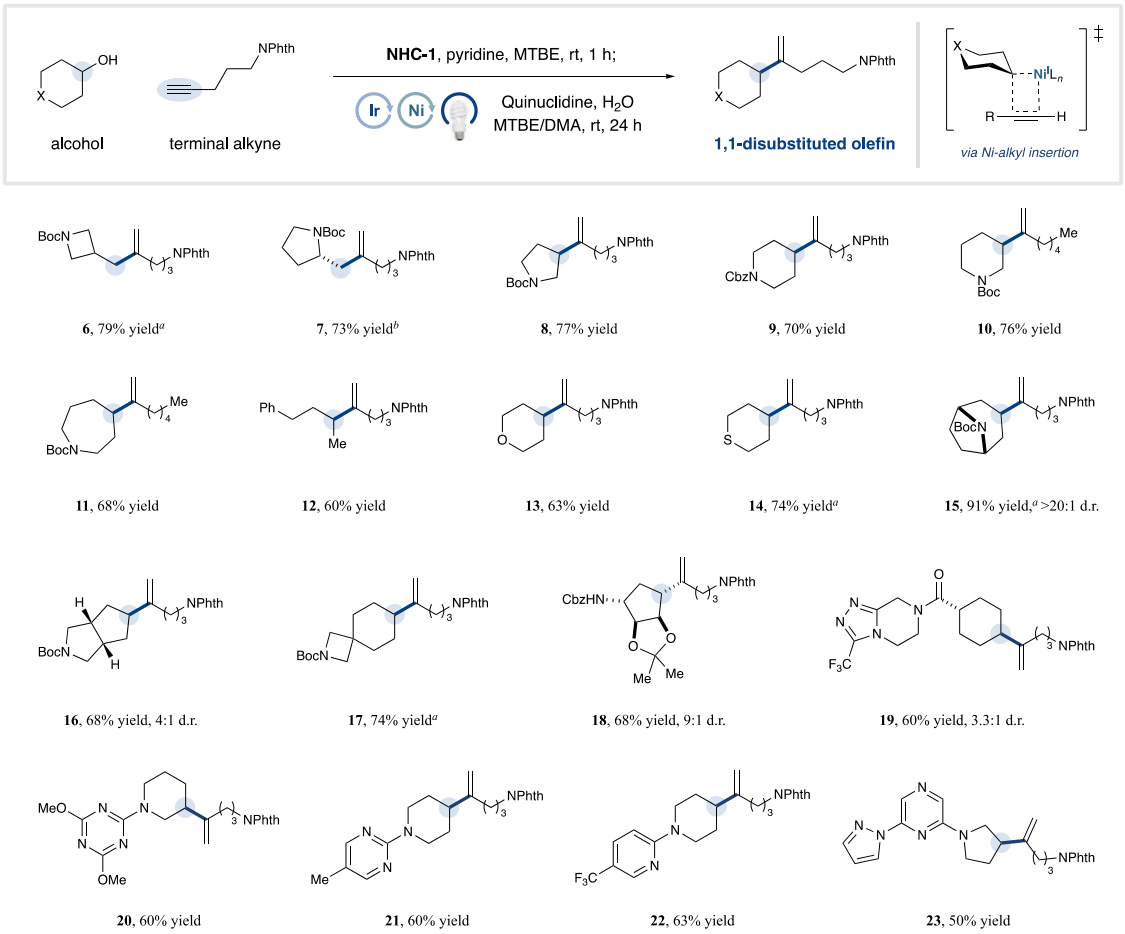


Figure 2. Alcohol scope for deoxygenative hydroalkylation of alkynes

Reactions typically performed using alcohol (1.65 equiv), **NHC-1** (1.5 equiv), pyridine (1.5 equiv) in MTBE (0.15 M) for 45–60 min, then **4** (2.0 mol %), $NiCl_2$(glyme) (15 mol %), **5** (17.5 mol %), quinuclidine (3 equiv), H_2O (40 equiv), alkyne (0.5 mmol, 1 equiv), and MTBE/DMA (1:1, 0.05 M) under IPR irradiation (450 nm) for 24 h. All yields isolated with r.r. >20:1. [a]Reagent and catalyst loading deviates; see the supplemental information for experimental details. Boc, *tert*-butoxycarbonyl; NPhth, *N*-phthalimido.

we expect this migratory insertion to proceed with a high degree of stereoselectivity and regioselectivity.[32,49] Protodemetallation then yields the desired olefin product **XIV** and regenerates the Ni(II) catalyst **V**.

Evaluation of alcohol scope

With optimal conditions in hand, we next evaluated the scope of the alcohol partner, using *N*-(4-pentynyl)phthalimide or 1-heptyne as the standard alkyne partner. We were pleased to observe that a range of alcohols could serve as viable coupling partners, affording complete selectivity for the desired 1,1-disubstituted olefins (Figure 2). Primary alcohols (**6** and **7**, 79% and 73% yield, respectively), cyclic secondary alcohols (**8–11**, 68%–77% yield), and an acyclic secondary alcohol (**12**, 60% yield) underwent efficient coupling to deliver hydroalkylated products. In addition to saturated nitrogen-containing heterocycles, tetrahydropyran and tetrahydrothiopyran moieties performed well (**13** and **14**, 63% and 74% yield, respectively), illustrating tolerance for distal oxidation-sensitive functionality. Alcohols containing various polycyclic substructures were also coupled in good to excellent yields (**15–17**, 68%–91% yield). Other biorelevant scaffolds, such as those based on acetal-protected unnatural sugars, were readily accommodated (**18**, 68% yield). Finally, we evaluated alcohol partners bearing medicinally relevant aromatic *N*-heterocyclic cores. Gratifyingly, triazolopiperazine (**19**, 60% yield), triazine (**20**, 60% yield), pyrimidine (**21**, 60% yield), and pyridine (**22**, 63% yield) moieties were well tolerated. Additionally, a scaffold containing three distinct aromatic heterocycles—pyrazole, pyrazine, and pyrrolidine—underwent coupling in modest yield (**23**, 50% yield; see Figure S46 in section 15 of the supplemental information for additional examples).

Evaluation of alkyne scope

We next evaluated the scope of the alkyne partner using alcohol **1** as the model coupling partner. As shown in Figure 3, good yields and excellent regioselectivities were achieved across a range of α-cyclic alkynes (**3** and **24–27**, 62%–85% yield). Alkynes bearing functional groups such as alkyl chlorides (**28**, 63% yield)

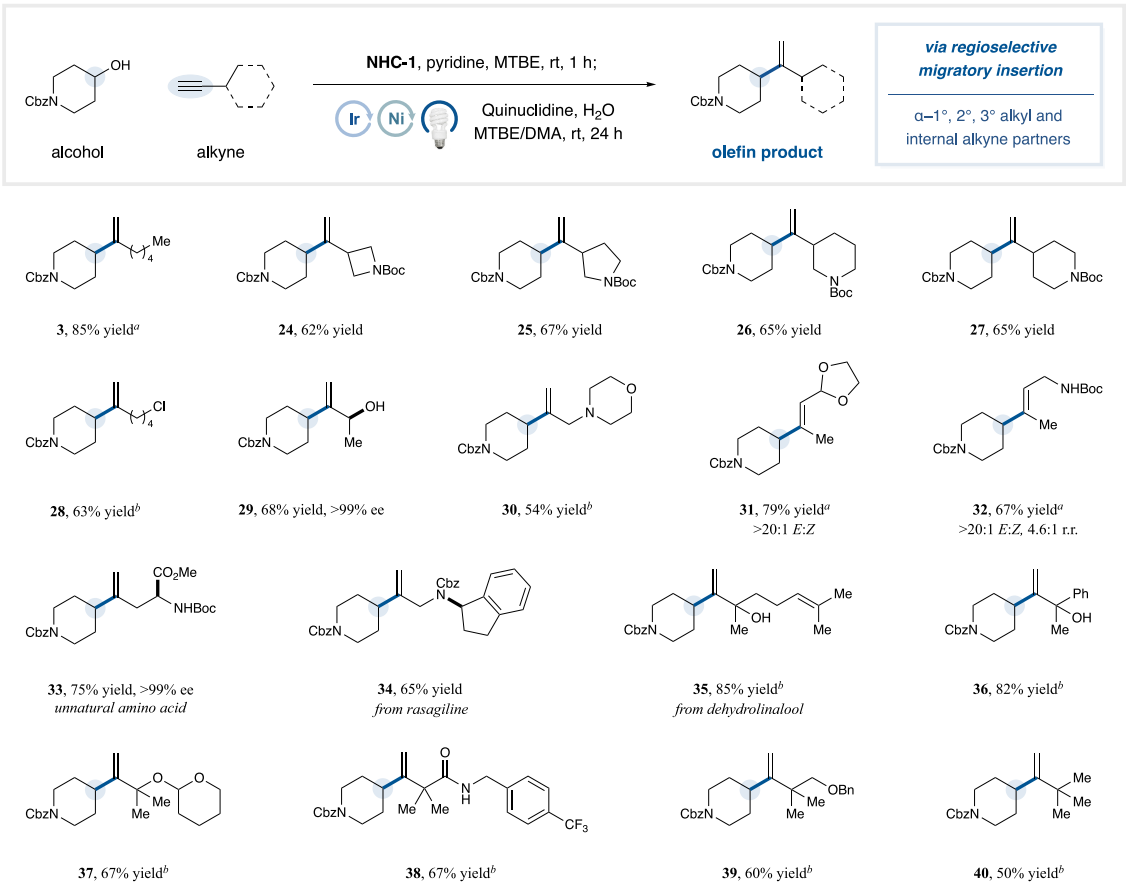


Figure 3. Alkyne scope for deoxygenative hydroalkylation of alkynes

All yields isolated with r.r. >20:1, unless otherwise indicated. See the supplemental information for experimental details. [a]Yield determined by ^{1}H NMR; see Figures S37, S38, S41, and S42 in section 13 of the supplemental information for details. [b]Reagent and catalyst loading deviates; see the supplemental information for experimental details.

and free alcohols (**29**, 68% yield, >99% ee; see Figures S39 and S40 in the supplemental information for more details) are well tolerated, highlighting both the selectivity of the reaction and the irreversibility of NHC activation of the desired alcohol partner. Additionally, the mild oxidation potential of the NHC-alcohol adduct allows selective oxidation even in the presence of sensitive functionalities such as morpholines (**30**, 54% yield).[40] This method also furnishes trisubstituted olefins. Unsymmetrical internal alkynes, which are traditionally challenging to functionalize regioselectively,[50] were successfully hydroalkylated to furnish trisubstituted olefins with good to excellent regioselectivity and yield (**31**, 79% yield, >20:1 *E*:*Z*, >20:1 r.r., and **32**, 67% yield, >20:1 *E*:*Z*, 4.6:1 r.r.). The observed regioselectivity is governed by alkyne polarity, with the nickel center preferentially positioned at the carbon of greatest electron density and the alkyl group situated at the more electrophilic carbon (see Figures S35 and S36 in section 9 of the supplemental information for more details on regioselectivity and ligand effects).[49] Biorelevant small molecules such as propargylalanine (**33**, 75% yield, >99% ee; see Figures S43 and S44 in the supplemental information for more details), a derivative of the MAO-B inhibitor rasagiline (**34**, 65% yield), and dehydrolinalool (**35**, 85% yield) proved to be competent partners, demonstrating tolerance for stereocenters and selective migratory insertion into alkyne π-systems over preexisting olefins. Lastly, we evaluated α-trisubstituted and α-tertiary alkynes, which require migratory insertion at sterically congested positions. A variety of α-trisubstituted and α-tertiary alkynes were successfully coupled to furnish hindered olefin products in modest to excellent yields, demonstrating tolerance for adjacent heteroatoms and providing access to structures that are not widely commercially available (**36–40**, 50%–82% yield; see Figures S47 and S48 in section 15 of the supplemental information for additional examples).

Late-stage hydroalkylation and downstream functionalization

We next explored the utility of this Markovnikov-selective hydroalkylation for the late-stage functionalization of complex molecules (Figure 4). Synthetic hormones, nucleobase analogs, and SSRI derivatives were successfully hydroalkylated in synthetically useful to excellent yields, demonstrating tolerance for sterically encumbered steroid ring systems (**41**, 87% yield), fused purine ring systems (**42**, 40% yield), and aryl fluorides (**43**, 73% yield). Moreover, hydroxyl-containing

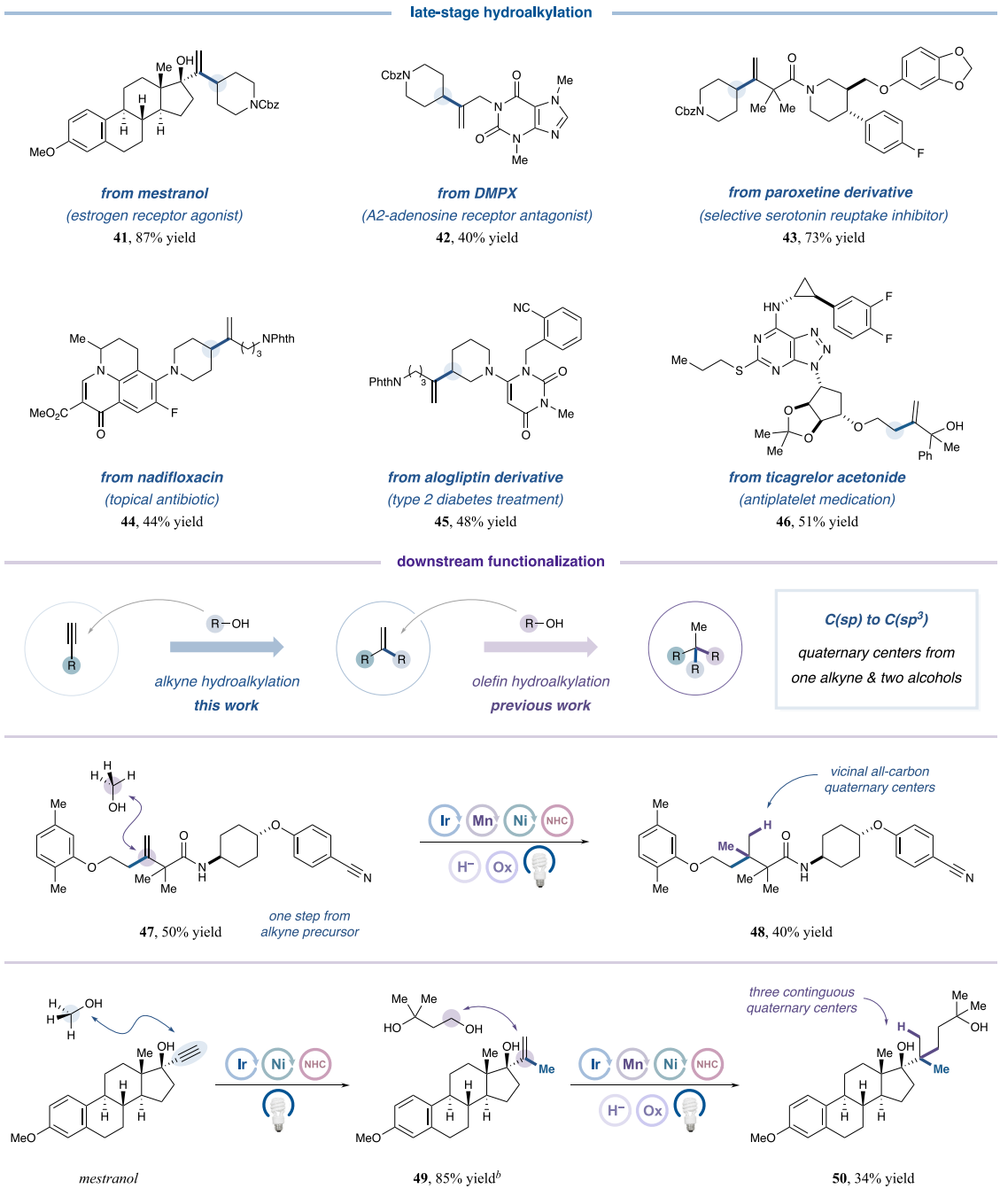


Figure 4. Late-stage hydroalkylation and downstream functionalization

All yields isolated with r.r. >20:1, unless otherwise indicated. See the supplemental information for experimental details. [a]Yield determined by ^{1}H NMR; see Figure S45 in section 14 of the supplemental information for details.

molecules derived from nadifloxacin, alogliptin, and ticagrelor served as competent alkylating partners (**44–46**, 44%–51% yield). To highlight the downstream synthetic utility of the 1,1-disubstituted olefin products, we next developed short synthetic sequences to rapidly convert alkyne starting materials into medicinally valuable scaffolds. All-carbon quaternary centers are desirable in drug candidates because they impart conformational rigidity and metabolic stability, yet they remain challenging to access under typical cross-coupling conditions.[8,51,52] We recently developed an MHAT metallaphotoredox method to create quaternary centers from olefins and alcohols via bimolecular homolytic substitution (S_H2).[53] We

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envisioned merging this olefin functionalization with our alkyne hydroalkylation to access quaternary centers from one alkyne and two alcohols through sequential deoxygenative hydroalkylations. Following the formation of 1,1-disubstituted olefin **47** (50% yield) from the corresponding alcohol and alkyne precursors, deoxygenative hydromethylation furnished AMPK agonist analog **48**—bearing vicinal all-carbon quaternary centers—in 40% yield.[54] In a parallel effort, the synthetic hormone mestranol underwent hydromethylation of the latent alkyne functionality to furnish olefin product **49** in an excellent 85% yield. Upon deoxygenative hydroalkylation with a short-chain diol, quaternary product **50** was obtained in 34% yield, demonstrating the capacity of this approach to generate three contiguous fully substituted carbon centers.

Conclusions

Collectively, these examples establish alcohol-derived alkyl radicals as effective partners in metallaphotoredox alkyne hydroalkylation, enabling direct access to sterically hindered olefin products from abundant alcohol feedstocks under mild conditions. This strategy substantially expands the scope of alkyne hydroalkylation, enabling the incorporation of complex functionality while accommodating sterically encumbered alkynes. Beyond serving as valuable molecular scaffolds, the resulting olefins can also undergo subsequent Markovnikov-selective hydroalkylation to furnish quaternary carbon centers, highlighting the utility of deoxygenative cross-couplings for the rapid assembly of densely substituted aliphatic frameworks.

METHODS

General procedure for deoxygenative hydroalkylation of alkynes

Alcohol solution (activated alcohol)

An oven-dried 40-mL vial was charged with **NHC-1** (296.4 mg, 0.75 mmol, 1.5 equiv), secondary alcohol (0.825 mmol, 1.65 equiv), and an X-shaped stir bar. The vial was evacuated and back-filled with N_2 (3 × 1 min). Methyl tert-butyl ether (MTBE) (5.00 mL, 0.15 M) was added via a syringe under nitrogen. This mixture was stirred briefly, and then pyridine (60.4 μL, 0.75 mmol, 1.5 equiv) was added slowly using a microsyringe. After pyridine addition, the N_2 line was removed, and the vial was sealed with parafilm. The heterogeneous mixture was vigorously stirred at room temperature for 45 to 60 min. During this time a white solid precipitated out, and the mixture either remained white or turned from white to pale pink.

Reaction vial

A second oven-dried 40-mL vial was charged with $[Ir(dtbppy)_2(bpy)]PF_6$ (10.69 mg, 0.010 mmol, 2 mol %), $NiCl_2$ glyme (16.5 mg, 0.075 mmol, 15 mol %), 4,4′-dimethoxy-2,2′-bipyridine (18.9 mg, 0.0875 mmol, 17.5 mol %), *N,N*-dimethylacetamide (DMA) (4.0 mL), and an X-shaped stir bar under air. The mixture was capped and sonicated to ensure homogeneity. After sonication, the mixture was sparged with N_2 for 1 h while stirring at 500 rpm.

Stock solution A

An oven-dried 8 mL vial was charged with quinuclidine (168 mg, 1.5 mmol, 3 equiv) and DMA (1.0 mL) under air. The mixture was sonicated to ensure homogeneity. After sonication, the mixture was placed in an ice bath, stirred, and sparged with N_2 for 1 h.

After completion of reaction vial and stock solution A sparging, the alcohol solution was filtered *under* N_2 into an oven-dried vial (also under N_2 atmosphere) using a 25-mm, Fisherbrand PTFE 0.2-μm syringe filter. Stock solution A (1.0 mL), deionized (DI) water (370 μL, 20 mmol, 40 equiv), filtered alcohol solution (5.0 mL), and alkyne (0.5 mmol, 1 equiv) were then added into the reaction vial. The reaction vial was sealed with electrical tape and melted parafilm and subjected to IPR irradiation using 450-nm LED modules at 10% light intensity, 5,200 rpm fan speed, and 500 rpm stir rate for 24 h. After this time, methyl 4-fluorobenzoate was added as an internal standard, and an aliquot was removed for nuclear magnetic resonance (NMR) analysis. Subsequently, the reaction mixture was transferred to a separatory funnel, and 30 mL of 10 wt % aqueous LiCl solution was added. The reaction vial was rinsed with EtOAc (40 mL total), and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (15 mL), dried over Mg_2SO_4, filtered, and concentrated *in vacuo*. The residue was subjected to automated column chromatography to afford the pure hydroalkylated products.

Other experimental details regarding the methods as well as characterization data can be found in the supplemental information.

RESOURCE AVAILABILITY

Lead contact

Requests for further information and resources should be directed to and will be fulfilled by the lead contact, David W.C. MacMillan (dmacmill@princeton.edu).

Materials availability

This study did not involve the design of unique reagents or catalysts for chemical synthesis.

Data and code availability

There is no dataset or code associated with this publication. All relevant procedures and experimental data are provided in the supplemental information.

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AUTHOR CONTRIBUTIONS

D.W.C.M. and I.M.M. conceived the research; I.M.M. designed the experiments, carried out the experiments, and analyzed the results under the guidance of D.W.C.M.; and I.M.M. and D.W.C.M. prepared the manuscript.

DECLARATION OF INTERESTS

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

SUPPLEMENTAL INFORMATION

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