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Direct Arylation of Strong Aliphatic C–H Bonds

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Despite the widespread success of transition metal-catalyzed cross-coupling methodologies, significant limitations still exist in reactions at sp^3-hybridized carbon atoms, with most approaches relying on prefunctionalized alkylmetal or bromide coupling partners[1,2]. While the use of native functional groups (e.g., carboxylic acids, alkenes, and alcohols) has improved the overall efficiency of such transformations by expanding the range of potential feedstocks[3–5], the direct functionalization of carbon-hydrogen (C–H) bonds—the most abundant moiety in organic molecules—represents a more ideal approach to molecular construction. In recent years, an impressive range of C(sp^3)-heteroatom bond forming reactions of strong C–H bonds have been reported[6,7]. Additionally, valuable technologies have been developed for the formation of carbon-carbon bonds from the corresponding C(sp^3)–H bonds via substrate-directed transition metal C–H insertion8, undirected C–H insertion by captodative rhodium carbenoid complexes9, or hydrogen atom transfer (HAT) from weak, hydridic C–H bonds by electrophilic open-shell species[10–14]. Despite these advancements, a mild and general platform for the coupling of strong, neutral C(sp^3)-H bonds with aryl electrophiles has not been realized. Here we describe a protocol for the direct C(sp^3) arylation of a diverse set of aliphatic, C–H bond-containing organic frameworks via the combination of light-driven, polyoxometalate-facilitated hydrogen atom transfer (HAT) and nickel catalysis. This dual-catalytic manifold enables the generation of carbon-centered radicals from strong, neutral C–H bonds, which thereafter act as nucleophiles in nickel-mediated cross-coupling with aryl bromides to afford sp^3-sp^2 cross-coupled products. This technology enables unprecedented, single-step access to a broad array of complex, medicinally relevant molecules directly from natural products and chemical feedstocks via functionalization at sites unreactive under traditional methods.

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Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Metallaphotoredox catalysis has recently emerged as an effective strategy for C(sp^3)–H functionalization[15]. Specifically, the merger of photoredox-mediated hydrogen atom transfer (HAT) and transition metal catalysis has delivered several methods for the selective functionalization of activated C–H bonds based on low bond dissociation energies (BDEs) and/or polarity effects (α-heteroatom, benzylic, and formyl)[10–14]. Inspired by these studies and a strong oxidant-mediated protocol for C(sp^3)–H arylation[16], we proposed that combining (i) an HAT catalyst capable of generating high-energy carbon-centered radicals from strong, inert C–H bonds with (ii) the elementary steps of nickel catalysis (aryl oxidative addition, reductive elimination) would allow, for the first time, the coupling of aliphatic carbon frameworks with a range of aryl bromide coupling partners.

We postulated that polyoxometalates (POMs), many of which possess high-energy excited states able to perform the desired C–H abstraction, would be ideal cocatalysts for the proposed transformation[17]. Of particular interest was the decatungstate anion ($[W_{10}O_{32}]^{4-}$), a POM which has been broadly utilized as an efficient HAT photocatalyst in a variety of oxygenations, dehydrogenations, conjugate additions, and, more recently, fluorinations of strong, unactivated, aliphatic C–H bonds[18–23] with BDEs up to 100 kcal mol^{-1}[24]. To our knowledge, the decatungstate anion has not previously been merged with transition metal cross-couplings, and we hoped that such a combination of catalytic processes would allow access to a significant breadth of carbon-centered radicals and aryl-functionalized products from abundant feedstocks (Figure 1). Furthermore, the observed selectivity of decatungstate for abstraction of electron-rich, sterically accessible C–H bonds[25] combined with the steric preference of nickel catalyzed cross-couplings suggested that our proposed dual-catalytic system could provide site-specific arylation of complex organic frameworks.

A detailed description of our proposed mechanism is illustrated in Figure 2. Photoexcitation of tetrabutylammonium decatungstate (TBADT, **1**) followed by intersystem crossing would produce the triplet excited state (**2**) (τ = 55 ns)[26]. Subsequent hydrogen atom abstraction from an alkyl nucleophile such as norbornane (**3**) by excited-state decatungstate (**2**) would readily afford singly-reduced decatungstate (**4**) and carbon-centered radical **5**. Disproportionation of singly-reduced decatungstate (**4**) would regenerate the active HAT photocatalyst **1** and concurrently form doubly reduced decatungstate (**6**)[26]. Two successive single-electron reductions of precatalyst $NiBr_2$•dtbbpy (dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) [E_p (Ni^{II}/Ni^0) = –1.47 V versus Ag/Ag^+ in MeCN, see Supplementary Information] by doubly-reduced decatungstate (**6**) [$E_{1/2}^{red}$ ($[W_{10}O_{32}]^{5-}/[W_{10}O_{32}]^{6-}$) = –1.52 V versus Ag/Ag^+ in MeCN, see Supplementary Information] could initially afford Ni^0 species **7**, which after capture of alkyl radical **5** would furnish Ni^I-alkyl species **8**. Subsequent oxidative addition into aryl halide **9** by Ni^I-alkyl species **8** would afford Ni^{III}(aryl)(alkyl) species **10**. Reductive elimination would provide desired cross-coupled product **11** as well as Ni^I species **12**. A final single-electron transfer step between this Ni^I species and the doubly-reduced polyoxometalate **6** would regenerate active Ni^0 catalyst **7**, as well as singly-reduced TBADT (**4**), closing both catalytic cycles. An alternative mechanism involving oxidative addition of Ni^0 catalyst **7** to aryl halide **9** could also be operative[27].

We began our investigation into the proposed transformation by exposing 5-bromo-2-trifluoromethylpyridine and cyclohexane to near-UV light [Kessil 34 W 390 nm light-

emitting diodes (LEDs)] in the presence of the commercially available HAT photocatalyst TBADT, $NiBr_2$•dtbbpy, and potassium phosphate in acetonitrile. To our delight we observed a 70% analytical yield of the desired cyclohexyl C–H arylation product. Critical to the success of the reaction was the exclusion of both oxygen and water (see Supplementary Information); however, the use of standard benchtop techniques was sufficient in this regard. Moreover, while five equivalents of the C–H nucleophile affords optimal yields, lower substrate loadings can be used albeit with diminished efficiency (see Supplementary Information).

With optimized conditions in hand, we next sought to examine the scope of the transformation with respect to the C–H bearing partner. As shown in Figure 3, a diverse array of organic frameworks proved to be competent coupling partners for the C–H arylation protocol. Cycloalkanes with various ring sizes ranging from five to eight carbons were arylated in good yields (**13** to **16**, 57 to 70% yield). Linear aliphatic systems were likewise successful in the protocol (**17** to **20**, 41 to 56% yield), with a greater-than-statistical preference observed for arylation of the less sterically demanding 2-position for all substrates, including *n*-hexane (**SI-1**, 48% yield, 60% selectivity). Electron-withdrawing substituents further improved this regiocontrol, highlighting the selectivity of decatungstate for more hydridic C–H bonds imparted by the electrophilic nature of its excited state[26]. Accordingly, we found ketones to be particularly effective in modulating regioselectivity, affording products functionalized distal to the electron-withdrawing carbonyl moiety (**21, 22, 31–35**, 31 to 65% yield).

This C–H arylation protocol was also found to effectively functionalize a range of electronically diverse primary and secondary benzylic C–H bonds, which were arylated in moderate to good yields (**23** to **25**, 62 to 71% yield, see Supplementary Information for three additional examples). Bridged bicyclic alkanes afforded arylated products with complete *exo*-selectivity (**26** to **29** and **35**, 40 to 67% yield), likely due to selective radical capture by nickel catalyst **7** on the less-hindered face. Functionalization of norbornane occurred selectively on the ethylene bridge (**26**, 61% yield). Notably, a bromide substitutent on the bridging methylene of norbornane was tolerated and, moreover, strongly influenced site-selectivity, giving only the *anti* product (**27**, 67% yield). Notably, heteroatom-containing bicycles afforded the desired products in moderate to good yields (**28** and **29**, 40 and 60% yield, respectively). Arylated lactam **29** was subsequently subjected to ring-opening reductive conditions to afford the carbocyclic nucleoside analogue **30** (94% yield), highlighting the utility of the C–H arylation protocol. Significantly, adamantane derivatives underwent arylation predominantly at the methylene position (**31** and **32**, 48 and 53% yield, respectively), an unexpected chemoselectivity given decatungstate-catalyzed adamantane functionalization affords 5:1 selectivity for methine positions when corrected for equivalent hydrogen atoms[28]. This result further highlights the role of the nickel catalyst in determining the regioselectivity of C–C bond formation, presumably via reversible radical capture and selectivity-determining reductive elimination[27]. Four-membered rings were also competent substrates for this arylation protocol, with both an exocyclic ketone and a spirocyclic ketone affording the desired product in moderate yields (**33** and **34**, 42 and 31% yield, respectively).

Tropinone, a common scaffold among natural products and pharmaceuticals[29], was also effectively subjected to this dual-catalysis protocol (**35**, 61% yield).

It is important to note that this transformation is not restricted to electronically neutral, unactivated C–H systems. Indeed, a variety of α-heteroatom C–H nucleophiles were readily modified with excellent regioselectivity. As follows from decatungstate's preference for the most hydridic and sterically accessible C–H bond, Boc-protected pyrrolidine was functionalized selectively at the α-amino position (**36**, 53% yield). Primary α-amino C–H nucleophile *N*-Boc dimethylamine also found to be an effective substrate for the transformation (**37**, 68% yield). In addition to nitrogen-containing nucleophiles, a variety of cyclic ethers were regioselectively functionalized in moderate to good yield at the α-oxy position (**38** to **43**, 48 to 70% yield). Notable among these substrates, alkyl halides were well-tolerated (**41** and **42**, 50 and 70% yield, respectively), opening avenues for subsequent synthetic manipulations. *N*-Boc-morpholine underwent C–H arylation predominantly at the α-amino C–H bond (**43**, 48% yield, 3.4:1 r.r.). Notably, useful amounts of the α-oxy product are generated in this case, in contrast to the quinuclidine-mediated triple catalytic arylation reported previously by our laboratory[10] (see Supplementary Information) as well as benzophenone-mediated cyanation[30], wherein exclusive α-amino functionalization is observed.

We next turned our attention to the scope of the aryl halide coupling partner. As shown in Figure 4, a broad range of electron-deficient aryl bromides provided the desired products in good yield (**44** to **49**, 60 to 70% yield). Furthermore, neutral and electron-rich substrates displayed useful coupling efficiencies (**50** to **54**, 52 to 62% yield). Chlorine- and fluorine-bearing aryl bromides were alkylated selectively as well (**55** and **SI-5**, 50 and 55% yield, respectively). Free alcohol-containing substrate **56** was also found to be a competent coupling partner (55% yield). *Ortho*-substituted aryl bromides were likewise alkylated in moderate to good yields (**57** and **58**, 45 and 71% yield, respectively). With respect to heteroaryl bromides, *N*-Boc-indole **59** underwent the desired transformation in useful efficiency (38% yield). A range of bromopyridines were alkylated in useful to good yields as well (**60** to **69**, 25 to 64% yield). Bromopyrimidines were effective substrates (**70** and **71**, 55 and 51% yield, respectively), and both electron-rich and electron-deficient 2-bromothiazoles afforded the desired product in moderate yields (**72** and **73**, 54 and 51% yield, respectively). Last, Celebrex precursor **74**, a pharmaceutically-relevant aryl halide, was subjected to the reaction conditions with a variety of alkyl C–H nucleophiles. Cyclohexane, cyclohexanone, and 7-bromonorbornane were all coupled in good efficiencies (**75a-c**, 60 to 67% yield), demonstrating the utility of the protocol in cross-coupling complex aryl fragments with structurally diverse C–H nucleophiles.

Having demonstrated the applicability of the C–H arylation protocol to a broad array of C–H nucleophiles and aryl halide electrophiles, we next investigated its efficacy on naturally occurring aliphatic systems. As illustrated in Figure 5a, a variety of inexpensive, abundant natural products were successfully functionalized under our standard conditions, enabling rapid arylation of complex stereo-defined frameworks at carbon sites that lack adaptive functional handles. Observed regioselectivities were in accordance with the expected preferences of this dual-catalytic manifold as described above. A moderate yield of

heteroarene coupled eucalyptol was observed (**76**, 55% yield), with a strong preference for arylation at the most hydridic and sterically accessible C–H bond. Useful efficiencies were observed for the terpene fenchone, which was also found to be a suitable substrate on 5.0 mmol scale (**77**, 38 and 41% yield, respectively. See Supplementary Information for experimental details). A free alcohol derivative of fenchone was also readily exploited in this protocol (**78**, 52% yield). Camphene, a terminal olefin-containing natural product, was also an effective substrate for arylation (**79**, 70% yield). Lastly, we sought to illustrate the generality of this method by derivatizing the lactone sclareolide with a range of aryl and heteroaryl bromides (**80a-c**, 35% to 43% yield). Notably, an alkyl acid chloride provided the sclareolide-derived ketone in useful efficiency (**80d**, 33% yield), illustrating the capability of our transformation to install a range of functionality onto complex aliphatic substrates without the need for directing groups.

Finally, we demonstrated the application of this C–H arylation protocol toward the rapid generation of complex pharmaceutically-relevant molecules. We set our sights on the natural product epibatidine, a potent non-opioid analgesic. Due to its high toxicity, epibatidine has seen limited potential as a commercial pharmaceutical[31]. However, a range of epibatidine analogues have been investigated in a clinical setting[32]. We first targeted the synthesis of (±)-*N*-Boc-epibatidine from commercially available 7-azabicyclo[2.2.1]heptane. When *N*-Boc-protected amine substrate **81** and 2-chloro-5-bromopyridine were subjected to the reaction conditions, we observed an unoptimized 28% yield of protected epibatidine (**82a**) in two steps from the commercially available unprotected amine (Figure 5b, see Supplementary Information for experimental details). To our knowledge, this is the shortest formal synthesis of (±)-epibatidine in the multitude of reported procedures to date[33]. Subsequently, we sought to demonstrate that diversification was possible by variation of both the alkyl fragment and the aryl bromide fragment. A representative sampling of heteroaryl bromides was coupled with bridged bicyclic amines to afford a small set of analogues in synthetically useful yields (**82b** to **83c**, 17 to 44% yield).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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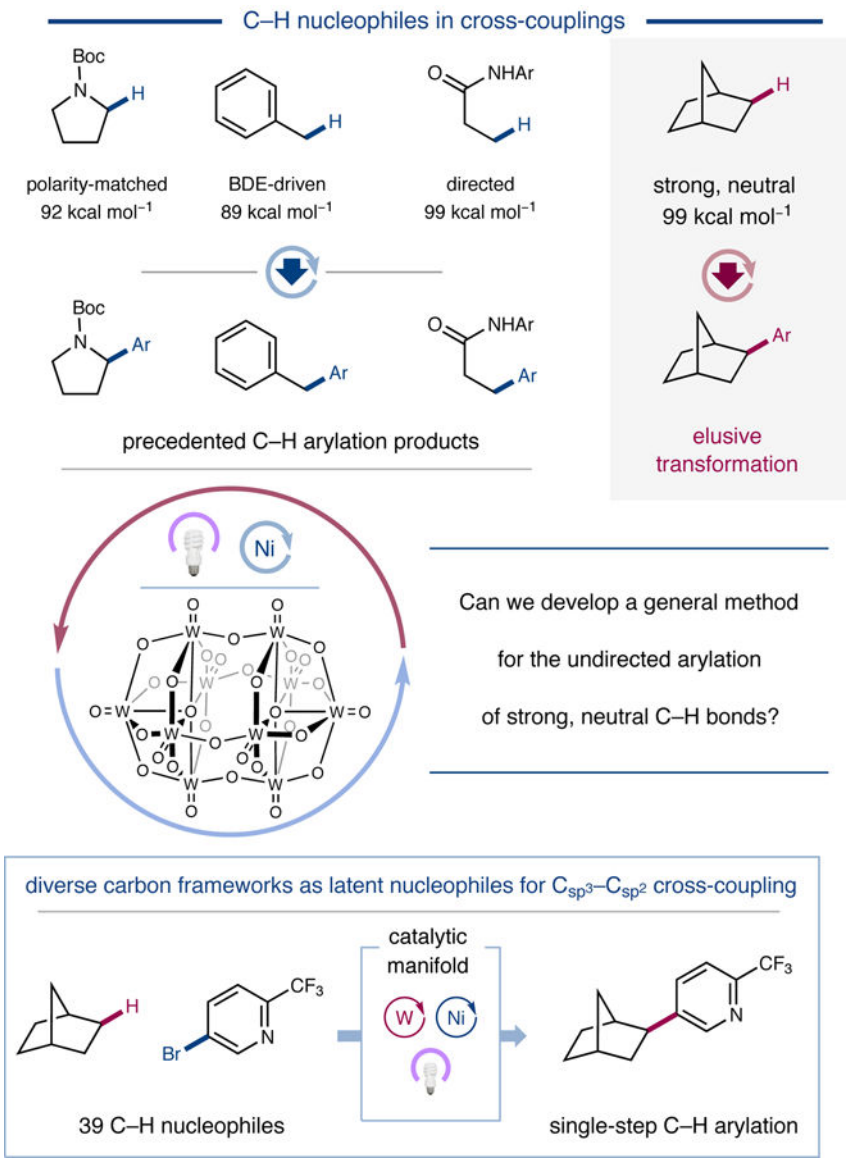

Figure 1 |. Undirected Aliphatic C–H Arylation.

Traditional transition metal-catalyzed C_{sp^3}–H arylation methods rely on adjacent or distal functionality to facilitate C–H bond activation (top). The use of a highly oxidizing polyoxometalate photocatalyst in combination with nickel catalysis enables direct arylation of strong, unactivated C–H bonds (bottom). Boc, *tert*-butoxycarbonyl; Ar, aryl; BDE, bond dissociation energy.

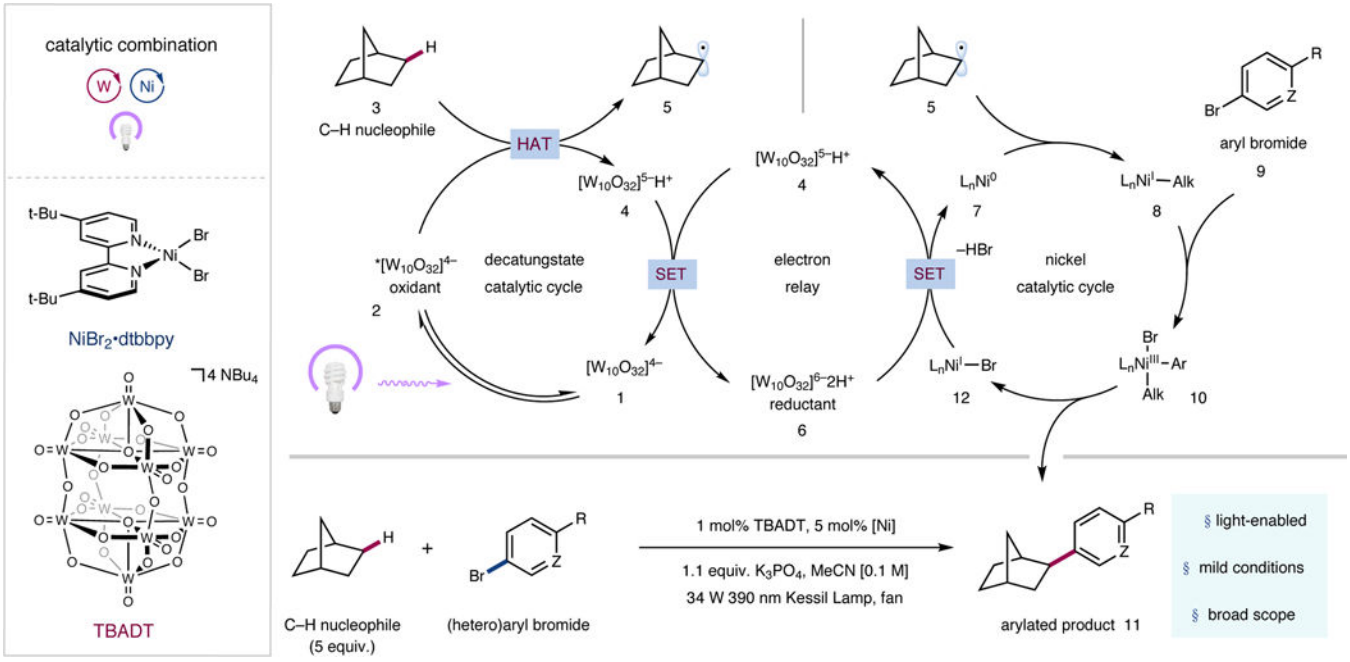

Figure 2 |. Reaction scheme and proposed mechanism for sp^3 C–H arylation via a dual polyoxometalate HAT and nickel catalytic manifold.

The catalytic cycle begins with photoexcitation of the decatungstate anion **1** to provide triplet excited state **2**. Hydrogen atom transfer (HAT) from nucleophile **3** affords reduced photocatalyst **4** and open-shell species **5**. Disproportionation of the reduced decatungstate species regenerates the active photocatalyst and affords the reducing hexa-anion **6**. Ni^0 species **7** subsequently captures alkyl radical **5**, furnishing Ni^I-alkyl species **8**. Oxidative addition into aryl electrophile **9** provides Ni^{III} species **10**, which undergoes reductive elimination to afford the product (**11**) and Ni^I–Br species **12**. Single electron transfer (SET) between **6** and **12** regenerates **7** and **4**, closing both catalytic cycles. dtbbpy, 4,4′-di-*tert*-butyl-2,2′-dipyridyl; TBADT, tetrabutylammonium decatungstate; Me, methyl; *t*-Bu, *tert*-butyl.

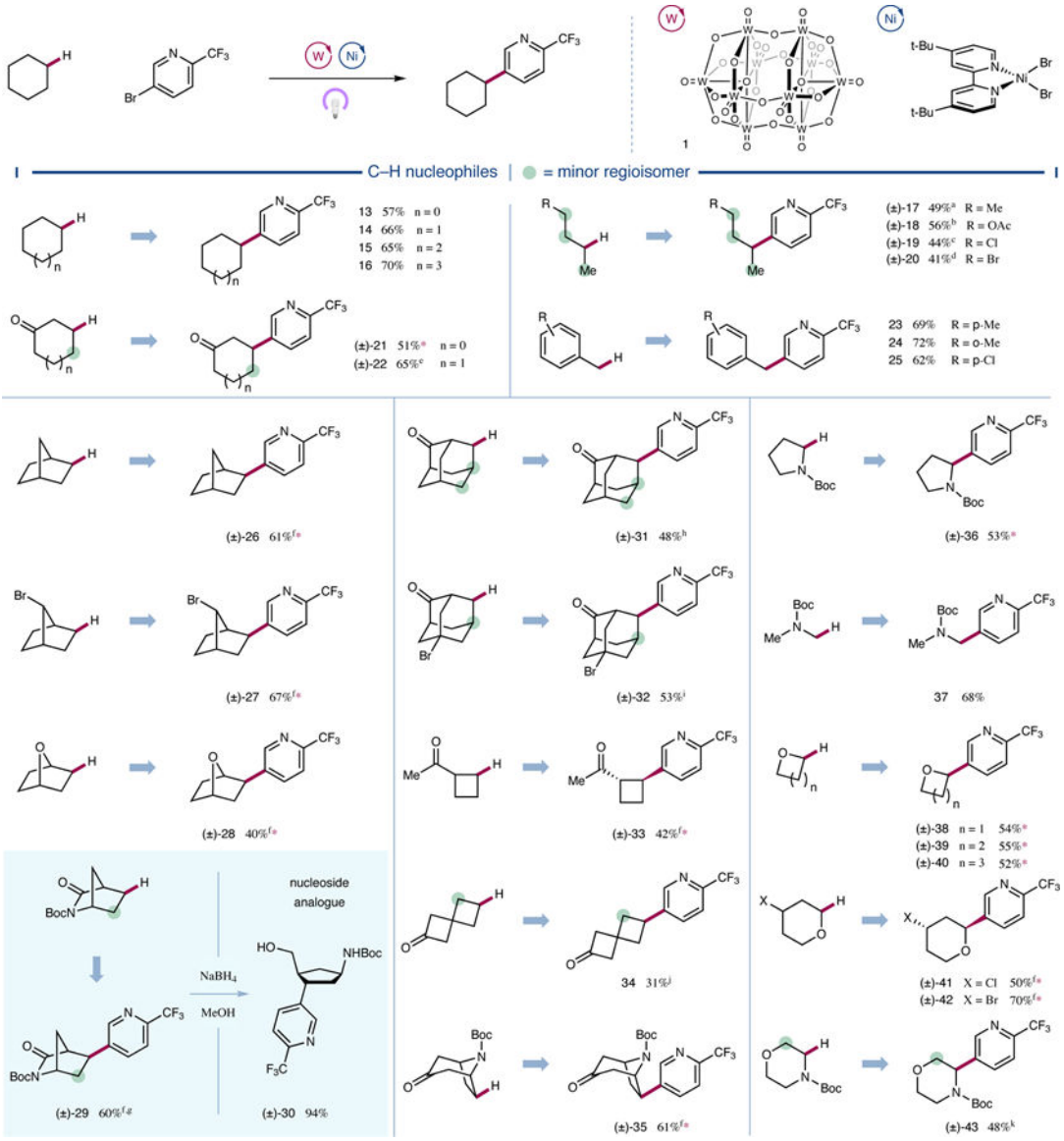

Figure 3 |. Scope of the alkyl nucleophile coupling partner.

A broad range of C–H nucleophiles are selectively functionalized by this arylation protocol. Cyclic, acyclic, and bicyclic aliphatic systems are amenable substrates. Heteroatom and carbonyl substituents electronically influence regioselectivity, and alkyl halides remain intact. All yields are isolated yields. Conditions as in Figure 2. Green circles denote sites where significant amounts of other regioisomers are observed. See Supplementary Information for experimental details. Ac, acetyl; d.r., diastereomeric ratio; r.r., regioisomeric ratio. *>20:1 r.r.; [a]70% selectivity; [b]53% selectivity; [c]79% selectivity; [d]93% selectivity; [e]1.4:1 r.r.; [f]>20:1 d.r; [g]2.5:1 r.r.; [h]79% selectivity, 3:1 d.r. (major); [i]1.8:1 r.r., 5.4:1 d.r. (major); [j]8.8:1 r.r.; [k]3.4:1 r.r.

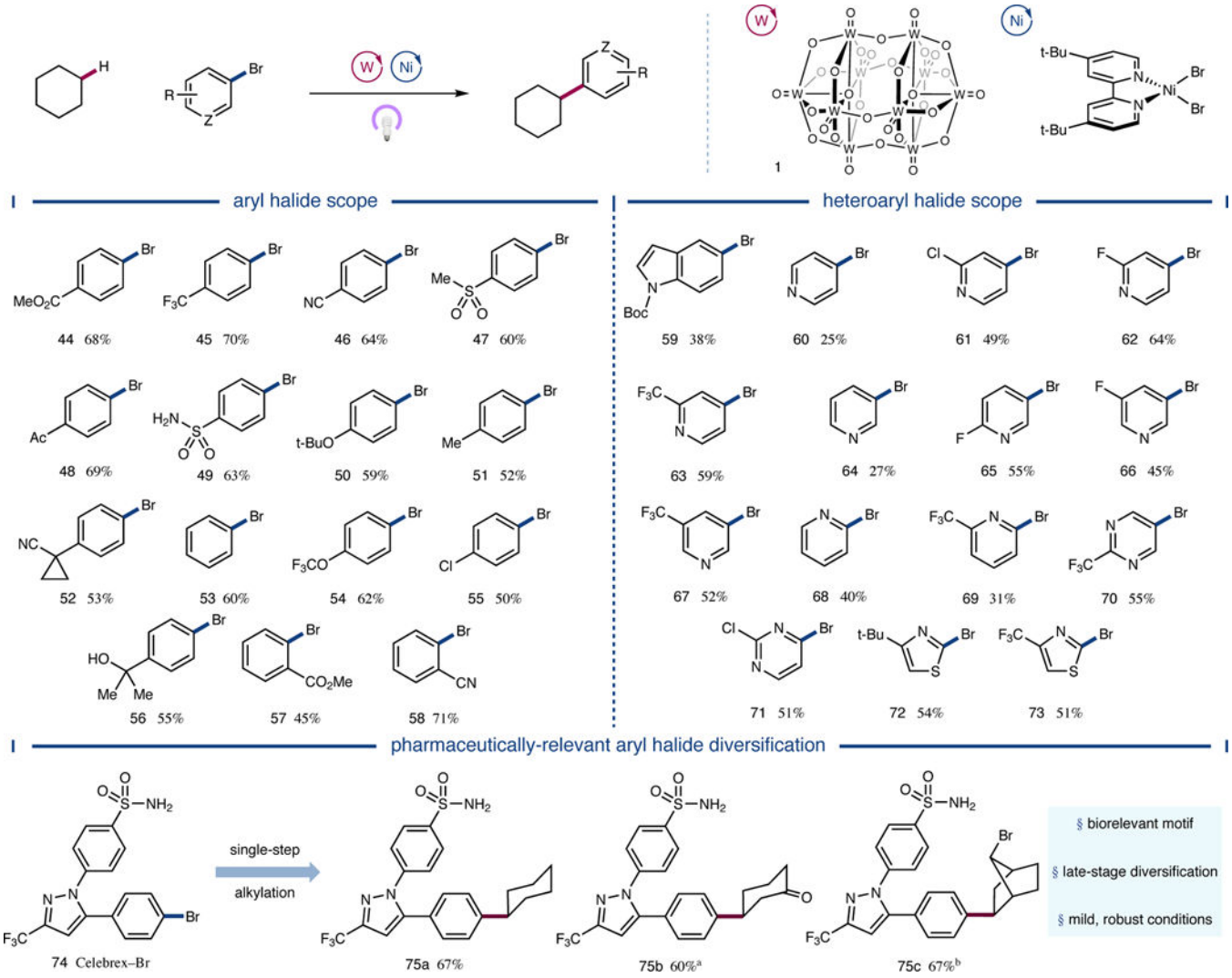

Figure 4 |. Scope of the aryl halide coupling partner.

A variety of electronically diverse aryl bromides were functionalized in moderate to good yields, and unprotected polar functionalities such as alcohols and sulfonamides were well tolerated. Moreover, heteroaryl bromides including indoles, pyridines, pyrimidines, and thiazoles were competent coupling partners in the transformation. Finally, the dual catalytic manifold was applied to the synthesis of several Celebrex analogues. All yields are isolated yields. Conditions as in Figure 2. See Supplementary Information for experimental details. [a]1.4:1 r.r.; [b]>20:1 d.r.

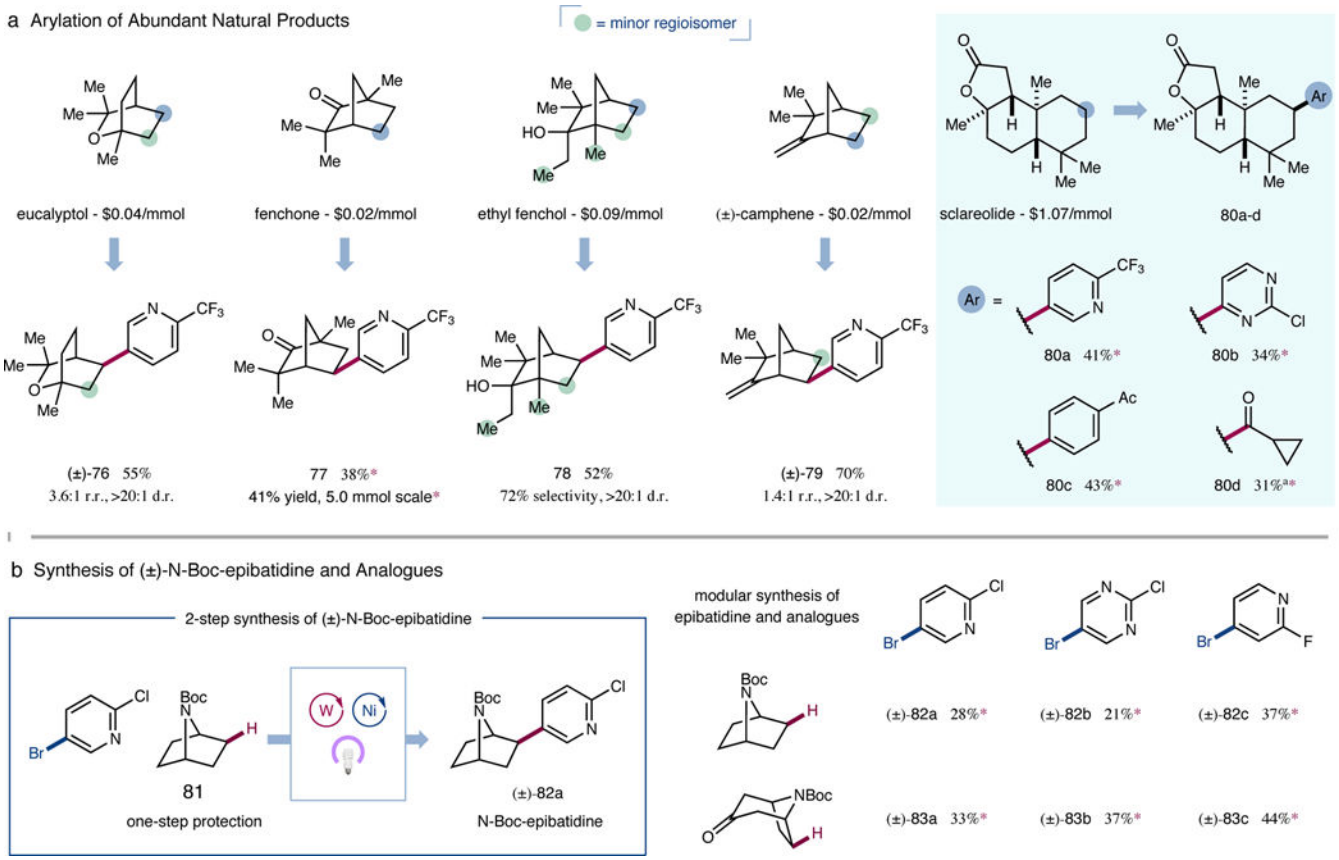

Figure 5 |. Functionalization, synthesis, and derivatization of natural products.

(**a**) A series of abundantly available terpenoids serve as competent coupling partners in this dual catalytic protocol, affording complex arylated scaffolds in good yields. Major and minor isomers are denoted. (**b**) The naturally occurring alkaloid (±)-*N*-Boc-epibatidine was synthesized in two steps from commercially available materials, and subsequently a small library of analogous compounds was constructed. *>20:1 r.r., >20:1 d.r.; [a]cyclopropane carbonyl chloride employed as electrophilic coupling partner.