Direct arylation of strong aliphatic C–H bonds

Ian B. Perry1,3, Thomas F. Brewer1,3, Patrick J. Sarver1, Danielle M. Schultz2, Daniel A. DiRocco2 & David W. C. MacMillan1*

Despite the widespread success of transition-metal-catalysed cross-coupling methodologies, considerable limitations still exist in reactions at sp3-hybridized carbon atoms, with most approaches relying on prefunctionalized alkylmetal or bromide coupling partners3–5. Although the use of native functional groups (for example, carboxylic acids, alkenes and alcohols) has improved the overall efficiency of such transformations by expanding the range of potential feedstocks3–5, 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 reactions that form C(sp3)–heteroatom bonds from strong C–H bonds has been reported6–7. Additionally, valuable technologies have been developed for the formation of carbon–carbon bonds from the corresponding C(sp3)–H bonds via substrate-directed transition-metal C–H insertion8, undirected C–H insertion by captodative rhodium carbenoid complexes9, or hydrogen atom transfer from weak, hydridic C–H bonds by electrophilic open-shell species10–14.

Despite these advances, a mild and general platform for the coupling of strong, neutral C(sp3)–H bonds with aryl electrophiles has not been realized. Here we describe a protocol for the direct C(sp3) arylation of a diverse set of aliphatic, C–H bond-containing organic frameworks through the combination of light-driven, polyoxometalate-facilitated hydrogen atom transfer and nickel catalysis. This dual-catalytic manifold enables the formation of carbon-centred radicals from strong, neutral C–H bonds, which thereafter act as nucleophiles in nickel-mediated cross-coupling with aryl bromides to afford C(sp3)–C(sp3) 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 through functionalization at sites that are unreactive under traditional methods.

Metallaphotoredox catalysis has recently emerged as an effective strategy for C(sp3)–H functionalization15. 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 and/or polarity effects (α-heteroatom, benzylic and formyl).10–14. Inspired by these studies and a strong oxidant-mediated protocol for C(sp3)–H arylation16, we proposed that combining a HAT catalyst capable of generating high-energy carbon-centred radicals from strong, inert C–H bonds with the elementary steps of nickel catalysis (aryl oxidative addition, reductive elimination) would enable the coupling of aliphatic carbon frameworks with a range of aryl bromide coupling partners.

We proposed 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 transformation17. Of particular interest was the decatungstate anion ([W10O32]4−), a POM that has been broadly used as an efficient HAT photocatalyst in various oxygenations, dehydrogenations, conjugate additions and, more recently, fluorinations of strong, unactivated, aliphatic C–H bonds18–23 with bond dissociation energies of up to 100 kcal mol−1 (for cyclohexane, ref. 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 enable access to a considerable breadth of carbon-centred radicals and aryl-functionalized products from abundant feedstocks (Fig. 1). Furthermore, the observed selectivity of decatungstate for the abstraction of electron-rich, sterically accessible C–H bonds17 combined with the steric preference of nickel-catalysed 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 Fig. 2. Photocexcitation of tetrabutylammonium decatungstate (TBADT; 1) followed by intersystem crossing would produce the triplet excited state (2) (with a lifetime, τ, of 55 ns)26. Subsequent hydrogen atom transfer from the triplet excited state of TBADT to the aryl bromide (3) would produce the excited state (4) of desired arylated product (5). At this point, strong, neutral C–H bonds can be generated through the formation of a Ni(0)–aryl radical intermediate (6), which is readily trapped by the POM cocatalyst (7). The excited state of POM (8) would then be generated through a rapid intersystem crossing, followed by a second HAT event with the aryl bromide (3) to afford the desired product (5).

Fig. 1 | Undirected aliphatic C–H arylation. a, Traditional transition-metal-catalysed C(sp3)–H arylation methods rely on adjacent or distal functionality to facilitate C–H bond activation. b, This dual-catalytic approach involves the combination of light-driven, polyoxometalate-facilitated hydrogen atom transfer and nickel catalysis. c, Use of this catalytic manifold enables the direct arylation of strong, unactivated C–H bonds. Ar, aryl; BDE, bond dissociation energy; Boc, tert-butoxycarbonyl.

1Merck Center for Catalysis at Princeton University, Princeton, NJ, USA. 2Department of Process Chemistry, Merck & Co., Inc., Rahway, NJ, USA. 3These authors contributed equally: Ian B. Perry, Thomas F. Brewer. *e-mail: dmacmill@princeton.edu

© 2018 Springer Nature Limited. All rights reserved.
abstraction from an alkyl nucleophile such as norbornane (3) by excited-state decatungstate (2) would readily afford singly reduced decatungstate (4) and carbon-centred radical 5. Disproportionation of singly reduced decatungstate (4) would regenerate the active HAT photocatalyst 1 and concurrently form doubly reduced decatungstate (6)25.

Two successive single-electron reductions of precatalyst Ni(dtbbpy)Br2 (dtbbpy = 4,4′-di-tert-butyl-2,2′-bipyridine) (E1/2 (NiIII/NiII) = −1.47 V versus Ag/AgCl in acetonitrile, see Supplementary Information) by doubly reduced decatungstate (6) (E1/2red ([W10O32]5−/ [W10O32]6−) = −1.52 V versus Ag/AgCl in acetonitrile, see Supplementary Information) could initially afford NiII species 7, which after capture of alkyl radical 5 would furnish NiI-alkyl species 8. Subsequent oxidative addition into aryl halide 9 by NiI-alkyl species 8 would afford NiII(aryl)(alkyl) species 10.

Reductive elimination would provide the desired cross-coupled product 11 as well as NiII species 12. A final single-electron transfer step between this NiII species and the doubly reduced polyoxometalate 6 would regenerate the active NiII catalyst 7, as well as singly reduced TBADT (4), closing both catalytic cycles. An alternative mechanism involving the oxidative addition of NiII 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-ultraviolet light (Kessil 34 W 390 nm light-emitting diodes (LEDs)) in the presence of the commercially available HAT photocatalyst TBADT, Ni(dtbbpy)Br2, 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, although 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 Fig. 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 (13–16, 57%–70% yield). Linear aliphatic systems were likewise successful in the protocol (17–20, 41%–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 on the ethylene bridge.26 Accordingly, we found ketones to be particularly effective in modulating regioselectivity, affording products that are functionalized distal to the electron-withdrawing carbonyl moiety (21, 22, 31–35, 31–65% yield).

This C–H arylation protocol was also found to effectively function- alize a range of electronically diverse primary and secondary benzylic C–H bonds, which were arylated in moderate to good yields (23–25, 62%–71% yield, see Supplementary Information for three additional examples). Bridged bicyclic alkanes afforded arylated products with complete exo-selectivity (26–29 and 35, 40%–67% yield), probably owing 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). A bromide substituent 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 carbocyclic nucleoside analogue 30 (94% yield), highlighting the utility of the C–H arylation protocol. Intriguingly, adamantane derivatives underwent arylation predominantly at the methylene position (31 and 32, 48% and 53% yield, respectively), an unexpected chemoselectivity given that decatungstate-catalysed adamantane functionalization affords 5:1 selectivity for methine positions when corrected for equivalent
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. 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, 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, various α-heteroatom C–H nucleophiles were readily modified with excellent regioselectivity. As follows from the preference of decatungstate for the most hydridic and sterically accessible C–H bond, tert-butoxycarbonyl...
Letter Research

Furthermore, neutral and electron-rich substrates displayed good yield. Notable among these substrates, alkyl halides 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 analogues of celecoxib. All yields are isolated yields. Conditions as in Fig. 2. See Supplementary Information for experimental details. *1:4.1 r.r., b 20:1 d.r.

Pharmaceutically relevant aryl halide diversification

(Aryl halide scope)

Boc-protected pyrrolidine was functionalized selectively at the α-amino position (36, 53% yield). Primary α-amino C–H nucleophile N-Boc dimethylamine was also found to be an effective substrate for the transformation (37, 68% yield). In addition to nitrogen-containing nucleophiles, various cyclic ethers were regioselectively functionalized in moderate to good yield at the α-oxy position (38–43, 48%–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 regioisomeric ratio (r.r.)). 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 laboratory10 (see Supplementary Information) as well as benzophenone-mediated cyanation30, wherein exclusive α-amino functionalization is observed.

We next turned our attention to the scope of the aryl halide coupling partner. As shown in Fig. 4, a broad range of electron-deficient aryl bromides provided the desired products in good yield (44–49, 60%–70% yield). Furthermore, neutral and electron-rich substrates displayed useful coupling efficiencies (50–54, 52%–62% yield). Chlorine- and fluorine-bearing aryl bromides were alkylated selectively as well (55 and 56, 50% and 55% yield, respectively), and 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 bromopyrimidines were alkylated in useful to good yields as well (60–62, 55%–57% 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). Lastly, the pharmaceutically relevant aryl halide 74, a precursor to celecoxib was subjected to the reaction conditions with various alkyl C–H nucleophiles. Cyclohexane, cyclohexanone and 7-bromonorbornane were all coupled in good efficiencies (75a–c, 60%–67% yield), which demonstrates 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.
and 2-chloro-5-bromopyridine were subjected to N-Boc-protected (−) epibatidine. We first targeted the synthesis of (−)-N-Boc-epibatidine from commercially available materials, and subsequently a small library of analogous compounds was constructed. A free-alcohol derivative of fenchone was also readily used in this protocol (80a–d), 38% and 41% yield, respectively; 77 for the terpene fenchone, which was also found to be a suitable substrate on 5.0-mmol scale (80b, 21%–44% yield). We have developed a robust method for the construction of C(sp3)–C(sp3) bonds from alkane nucleophiles and aryl bromide electrophiles. We believe that these results demonstrate the potential to use unactivated C–H bonds as nucleophiles in transition-metal-catalysed cross-coupling reactions. Finally, we demonstrated the application of this C–H arylation protocol towards the rapid generation of complex pharmaceutically relevant molecules. Our target was the natural product epibatidine, a potent non-opioid analgesic. Owing to its high toxicity, epibatidine has been limited potential as a commercial pharmaceutical; however, a range of epibatidine analogues has been investigated in a clinical setting. Limited potential as a commercial pharmaceutical, but a range of heteroaryl-coupled eucalyptol was observed (76, 55% yield), of which 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 bonds as nucleophiles in transition-metal-catalysed cross-coupling reactions using alkyl-organometallics as reaction partners. As illustrated in Fig. 5a, various inexpensive, abundant natural products were successfully functionalized under our standard conditions, enabling the rapid arylation of complex stereodefined frameworks at carbon sites that lack adaptive functional handles. The observed regioselectivities were in accordance with the expected preferences of these results demonstrate the potential to use unactivated C–H bonds as nucleophiles in transition-metal-catalysed cross-coupling reactions. Lastly, we sought to illustrate the generality of this method by derivatizing the lactone sclareolide with a range of aryl and heteroaryl bro-mides (80a–c, 35%–43% yield). Notably, an alkyl acid chloride provided the sclareolide-derived ketone in useful efficiency (80d, 33% yield), which illustrates 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 towards the rapid generation of complex pharmaceutically relevant molecules. Our target was the natural product epibatidine, a potent non-opioid analgesic. Owing to its high toxicity, epibatidine has been limited potential as a commercial pharmaceutical; however, a range of epibatidine analogues have been investigated in a clinical setting. 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 (Fig. 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. 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, 21%–44% yield). We have developed a robust method for the construction of C(sp3)–C(sp3) bonds from alkane nucleophiles and aryl bromide electrophiles. We believe that these results demonstrate the potential to use unactivated C–H bonds as nucleophiles in transition-metal-catalysed cross-coupling transformations.

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

Received: 20 April 2018; Accepted: 6 June 2018;
Published online 1 August 2018.

1. Jana, R., Phathak, T. P. & Sigman, M. S. Advances in transition metal (Pd, Ni, Fe)-catalyzed cross-coupling reactions using alkyl-organometallics as reaction partners. Chem. Rev. 111, 1417–1492 (2011).
2. Tasker, S. Z., Standley, E. A. & Jamison, T. F. Recent advances in homogeneous nickel catalysis. Nature 509, 299–309 (2014).
3. Zuo, Z. & MacMillan, D. W. C. Decarboxylative arylation of α-amino acids via photoredox catalysis: a one-step conversion of biomass to drug pharmacophore. J. Am. Chem. Soc. 136, 5257–5260 (2014).
4. Lo, J. C., Gui, J., Yabe, Y., Pan, C.-M. & Baran, P. S. Functionalized olefin cross-coupling to construct carbon–carbon bonds. Nature 516, 343–348 (2014).
7. Karimov, R. R. & Hartwig, J. F. Transition-metal-catalyzed selective functionalization of C(sp^3)-H bonds in natural products. Angew. Chem. Int. Ed. 57, 4234–4241 (2018).

8. He, J., Wasa, M., Chan, K. S. L., Shao, Q. & Yu, J.-Q. Palladium-catalyzed functionalization of C(sp^3)-H bonds in natural products. J. Am. Chem. Soc. 137, 13862–13867 (2015).

9. Liao, K., Negretti, S., Musaev, D. G., Bacsa, J. & Davies, H. M. L. Site-selective and stereoselective functionalization of unactivated C-H bonds. Nature 533, 230–234 (2016).

10. Shaw, M. H., Shurtleff, V. W., Terrett, J. A., Cuthbertson, J. D. & MacMillan, D. W. C. Alcohols as latent coupling fragments for the combination of nickel, hydrogen atom transfer, and photoredox catalysis. J. Am. Chem. Soc. 138, 11353–11356 (2016).

11. Le, C., Liang, Y., Evans, R. W., Li, X. & MacMillan, D. W. C. Selective C-H allylation via polarity-match-based cross-coupling. Nature 547, 79–83 (2017).

12. Zhang, X. & MacMillan, D. W. C. Direct aldehyde C-H arylation and alkylation via the combination of nickel, hydrogen atom transfer, and photoredox catalysis. J. Am. Chem. Soc. 139, 12715–12718 (2016).

13. Shields, B. J. & Doyle, A. G. Direct C(sp^3)-H cross coupling enabled by catalytic generation of chlorine radicals. J. Am. Chem. Soc. 138, 12719–12722 (2016).

14. Twilton, J. et al. The merger of transition metal and photocatalysis. Nat. Rev. Chem. 1, 0052 (2017).

15. Liu, D. et al. Nickely-catalyzed selective oxidative radical cross-coupling: an effective strategy for inert Csp^3-H functionalization. Org. Lett. 17, 998–1001 (2015).

16. Hill, C. L. & Prosser-McCarth, C. M. in Photodissensitization and Photocatalysis Using Inorganic and Organometallic Compounds (eds Kalyanasundaram, K. & Grätzel, M.) 307–330 (Springer, Dordrecht, 1993).

17. Renneke, R. F. & Hill, C. L. Homogeneous catalytic photochemical functionalization of alkynes by polyoxometalates. J. Am. Chem. Soc. 108, 3528–3529 (1986).

18. Renneke, R. F. & Hill, C. L. Selective photochemical dehydrogenation of saturated hydrocarbons with quantum yields approaching unity. Angew. Chem. Int. Ed. Engl. 27, 1526–1527 (1988).

19. Raveilli, D., Pratti, S. & Fagnoni, M. Decatungstate anion for photocatalysis: “window ledge” reactions. Acc. Chem. Res. 49, 2232–2242 (2016).

20. Schultz, D. M. et al. Oxyfunctionalization of the remote C-H bonds of aliphatic amines by decatungstate photocatalysis. Angew. Chem. Int. Ed. 56, 15274–15278 (2017).

21. Halperin, S. D. et al. Development of a direct photocatalytic C-H fluorination for the preparative synthesis of odanacatib. Org. Lett. 17, 5200–5203 (2015).

22. West, J. G., Huang, D. & Sorensen, E. J. Acceptorless dehydrogenation of small molecules through cooperative base metal catalysis. Nat. Commun. 6, 10093 (2015).

23. Luo, Y.-R. Handbook of Bond Dissociation Energies in Organic Compounds (CRC Press, Boca Raton, 2003).

24. Raveilli, D., Fagnoni, M., Fukuyama, T., Nishioka, T. & Ryu, I. Site-selective C-H functionalization by decatungstate anion photocatalysis: synergistic control by polar and steric effects expands the reaction scope. ACS Catal. 8, 701–713 (2018).

25. De Waele, V., Poizat, O., Fagnoni, M., Bagno, A. & Raveilli, D. Unraveling the key features of the reactive state of decatungstate anion in hydrogen atom transfer (HAT) photocatalysis. ACS Catal. 6, 7174–7182 (2016).

26. Gutierrez, O., Tellis, J. C., Primer, D. N., Molander, G. A. & Kozlowski, M. C. Nickel-catalyzed cross-coupling of photocatalyst-generated radicals: uncovering a general manifold for stereocconvergence in nickel-catalyzed cross-couplings. J. Am. Chem. Soc. 137, 4896–4899 (2015).

27. Ermolenko, L. P. & Giannotti, C. Aerobic photocatalysed oxidation of alkane in the presence of decatungstates: products and effects of solvent and counter-ion of the catalyst. J. Chem. Soc. Perkin Trans. 2 6, 1205–1210 (1996).

28. Grynkiewicz, G. & Gadzikowska, M. Tropane alkaloids as medicinally useful natural products and their synthetic derivatives as new drugs. Pharmacol. Rep. 60, 439–463 (2008).

29. Hoshikawa, T., Yoshikawa, S., Kamiyo, S. & Inoue, M. Photoinduced direct cyanation of C(sp^3)-H bonds. Synthesis 45, 874–887 (2013).

30. Bannon, A. W. et al. Broad-spectrum, non-opioid analgesic activity by selective modulation of neuronal nicotinic acetylcholine receptors. Science 279, 77–80 (1998).

31. Badio, B., Garraffo, H. M., Plummer, C. V., Padgett, W. L. & Daly, J. W. Synthesis and nicotinic activity of epiboxidine: an isoxazole analogue of epibatidine. Eur. J. Pharmacol. 321, 189–194 (1997).

32. de Oliveira Filho, R. E. & Omori, A. T. Recent syntheses of frog alkaloid epibatidine. J. Braz. Chem. Soc. 26, 837–850 (2015).

Acknowledgements The research reported here was supported by the National Institutes of Health National Institute of General Medical Sciences (RO1 GM105358-03) and gifts from MSD, Bristol-Myers Squibb, Eli Lilly, Genentech, Pfizer and Johnson & Johnson. The authors thank C. Kraml, N. Byrne and L. Wilson (Lotus Separations) for compound purification and I. Pelczer for assistance in structure determination.

Author contributions I.B.P., T.F.B., P.J.S., D.M.S., D.A.D. and D.W.C.M. designed the experiments. I.B.P., T.F.B., P.J.S. and D.M.S. performed and analysed the experiments. I.B.P., T.F.B., P.J.S., D.A.D. and D.W.C.M. prepared the manuscript.

Competing interests The authors declare no competing interests.

Additional information Supplementary information is available for this paper at https://doi.org/10.1038/s41586-018-0366-x.

Reprints and permissions information is available at http://www.nature.com/reprints.

Correspondence and requests for materials should be addressed to D.W.C.M.

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.