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Metal-catalysed cross-couplings are a mainstay of organic synthesis and are widely used for the formation of C-C bonds, particularly in the production of unsaturated scaffolds[1]. However, alkyl cross-couplings using native sp^3-hybridized functional groups such as alcohols remain relatively underdeveloped[2]. In particular, a robust and general method for the direct deoxygenative coupling of alcohols would have major implications for the field of organic synthesis. A general method for the direct deoxygenative cross-coupling of free alcohols must overcome several challenges, most notably the in situ cleavage of strong C–O bonds[3], but would allow access to the vast collection of commercially available, structurally-diverse alcohols as coupling partners[4]. We report herein a metallaphotoredox-based cross-coupling platform in which free alcohols are activated in situ by N-heterocyclic carbene salts for carbon-carbon bond formation with aryl halide coupling partners. This method is mild, robust, selective, and most importantly, capable of accommodating a wide range of primary, secondary, and tertiary alcohols as well as pharmaceutically-relevant aryl and heteroaryl bromides and chlorides. The power of the transformation has been demonstrated in a number of complex settings, including the late-stage functionalization of Taxol and a modular synthesis of Januvia, an antidiabetic medication. This technology represents a general strategy for the merger of in situ alcohol activation with transition metal catalysis.

Over the past half century, advances in transition metal-catalyzed cross-coupling have revolutionized the field of synthetic chemistry, enabling the rapid diversification of simple, abundant starting materials as well as the late-stage modification of highly complex molecular architectures[1,5]. Synthetic chemists today can select from a wide range of cross-coupling methods to gain easy access to unsaturated scaffolds from sp^2-hybridized coupling partners[6]. However, significant limitations remain with respect to the activation and coupling of sp^3-hybridized substrates[2]. Despite notable recent advances in the use of bench-stable sp^3-hybridized coupling partners, such as carboxylic acids[7] and alkyl halides[8,9], the most abundant and versatile alkyl source—the alcohol—remains underdeveloped[10] (Fig. 1a).

The alcohol is a well-established 'native' functional group, remarkably widely represented in commercially available sources and pharmaceutically relevant molecules[11]. A general method by which to accomplish direct deoxygenative alcohol cross-coupling would allow unparalleled entry into a vast new collection of diverse substrates. To date, however, no general strategy for the direct cross-coupling of alcohols has been reported. Attempts to achieve alcohol cross-coupling have been beset by both scope limitations and significant issues of substrate generality[10,12–14], often arising from the difficult C(sp^3)–OH cleavage step. Although kinetically-facile homolytic deoxygenation methods are well-known, these methods often rely on main group elements, such as phosphorus[15] and sulfur[16] that cannot be generically merged with transition metal catalysis[17]. As an alternative, the alcohol coupling partner may be pre-activated prior to introduction to the cross-coupling reaction, although this process requires additional chemical steps and purifications[18–20]. We recognized that, in order to truly harness the potential of alcohol substrates for cross-couplings, it would be necessary to conceive of a new alcohol activation strategy that would allow direct deoxygenative coupling of a diverse array of sp^3-hybridized alcohols. Ideally, this new activation mode should: (1) require no separate alcohol pre-activation step, (2) be amenable to all classes of alkyl alcohol substrates, (3) be readily adaptable across diverse transition metal-based cross-coupling platforms, and (4) exhibit exceptional levels of functional group tolerance. To demonstrate this conceptually novel disconnection as a generic platform for metal-mediated transformations, we have elected to perform deoxygenative arylation with pharmaceutically relevant aryl halides as coupling partners.

From the outset, we recognized that a fundamental challenge would involve the *in situ* alcohol activation prior to C(sp^3)–O bond cleavage. In order to accommodate a diverse range of chemical complexity and substrate C–O bond strengths, this activation step would require a significant thermodynamic driving force, as well as a kinetically-facile, exothermic C(sp^3)–O bond homolysis step. Along these lines, we took note of reports that *N*-heterocyclic carbenes (NHCs) undergo reversible condensation with the polar O–H bond[21]. We envisioned that subsequent oxidation of the electron-rich NHC–alcohol adduct should provide an exothermic pathway for the formation of a benign aromatic byproduct, thereby providing a strong driving force for C(sp^3)–O homolytic bond cleavage. Based on recent investigations into α-amino C–H bond homolysis by our group[22] and others[23], we anticipated using photoredox

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catalysis to selectively generate the open-shell NHC–alcohol intermediate via sequential single electron transfer (SET) and proton transfer (PT) events. Photoredox activation would also provide a general platform to interface the oxidatively-generated carbon-centered radicals with a variety of transition metal-catalyzed transformations (Fig. 1b). As an important design criteria, we hoped to exploit the NHC–alcohol motif as an efficient quencher of excited state photocatalysts, given the ultra-fast rate at which anilinic systems are known to undergo SET with established photocatalysts[22]. Beyond rapid C–O bond homolysis, such a system would further allow chemoselective oxidation of the NHC adduct in the presence of prototypical medicinal chemistry moities such as carboxylates and tertiary amines, thereby ensuring broad functional group tolerance. On this basis, we herein report the development of a nickel metallaphotoredox-catalyzed deoxygenative arylation of alcohols with aryl halide electrophiles. (Fig. 1c).

The proposed mechanism for the deoxygenative arylation is outlined in Fig. 2a. An alcohol substrate (**1**) condenses with a benzoxazolium salt (**2**) to form a NHC–alcohol adduct (**3**) under mild, basic conditions. Excitation of photocatalyst $[Ir(ppy)_2(dtbbpy)](PF_6)$ (**4**, ppy = 2-phenylpyridine, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) under blue light is known to generate the long-lived triplet-excited state Ir^{III*} complex (**5**, with a lifetime, τ, of 1.3 μs)[24]. This excited-state Ir complex ($E_{1/2}^{red}[Ir^{III*}/Ir^{II}]$ = + 0.66 V vs. SCE) can readily oxidize the anilinic nitrogen atom in **3** via a single electron transfer mechanism[22]. The C–H bond adjacent to the resulting nitrogen radical cation intermediate (**7**), now significantly weakened and more acidic (pKα ≈10)[25], can be deprotonated by a suitable base to yield an α-amino radical (**8**). This unique carbon-centered radical **8**, located adjacent to three heteroatoms, should undergo rapid β-scission to give carbamate **9**[26,27], and deoxygenated alkyl radical **10**. Importantly, formation of this aromatized carbamate byproduct (**9**), possessing a strong C=O double bond, is anticipated to provide a universal thermodynamic driving force for alcohol C–O bond homolysis. In the nickel catalytic cycle, the Ni(0) species **12**, generated from a Ni(II) precatalyst via two sequential SET events with reduced photocatalyst **6** ($E_{1/2}^{red}[Ir^{III}/Ir^{II}]$ = -1.51 V vs. SCE)[23], is expected to undergo facile oxidative addition into an aryl bromide (**13**) to form an aryl Ni(II) species (**14**). Trapping of the alcohol-derived radical species **10** by **14** should yield the key Ni(III) species **15**. Finally, reductive elimination from the Ni(III) metal center forges the requisite C–C bond, delivering the deoxygenative arylation product **16** and expelling the Ni(I) intermediate **11**, thereby simultaneously completing both the photoredox and the nickel catalytic cycle.

With this working hypothesis in hand, we first sought to identify suitable NHC salts. One major challenge is the propensity of the NHC–alcohol adduct to transfer a free NHC ligand to the metal center and release the alcohol, owing to the reversible, dynamic nature of the NHC–alcohol bond.[28] Upon extensive screening of NHC salts, we found a highly electron-deficient precursor *N*-aryl benzoxazolium salt (**17**)[29] to be an effective activating agent, delivering the desired deoxygenative coupling product (**16**) in 72% yield. In contrast, other common NHC salts—such as benzimidazolium (**18**)[30], benzothiazolium (**19**), and triazolium salts (**20**)[31] failed to produce the desired product (Fig. 2b). For a detailed rationale of this unique NHC skeleton preference, see SFig. 7 and SFig. 8. Modifications to the benzoxazolium backbone revealed modified NHC salt **2** to be highly effective at activating alcohol **1** for cross-coupling. Based on previous studies, the benzoxazolium- based free carbene represents the most electron-deficient NHC synthesized to date[32]. We hypothesize that the electron-deficient nature of the NHC significantly decreases the tendency of the NHC-alcohol adduct (**3**) to dissociate. Indeed, we did not observe **3** undergo dynamic exchange with other alcohols or metal catalysts under reaction conditions, which is opposite to the reported behavior of more electron-rich NHC-alcohol adducts[21,28]. More surprisingly, the benzoxazolium salt **2** readily condensed with alcohols in less than 5 minutes with high efficiency in ethereal solvents. The resulting solution of NHC-alcohol adduct **3** can be directly mixed with the aryl halide, 1.5 mol% $Ir(ppy)_2(dtbbpy)PF_6$, and 5 mol% $Ni(dtbbpy)Br_2$ as catalysts, 1.5 equivalents of quinuclidine as base, without isolation or purification of compound **3**. Upon 450 nm blue light irradiation of the crude reaction mixture, the desired adduct **16** was obtained in 88% yield. As an important design component, we were satisfied to find that NHC-alcohol adduct **3** does indeed quench the excited state photocatalyst **5** significantly faster than a number of medicinal chemistry functionalities that can be susceptible to SET, including carboxylates and tertiary amines (Fig. 2c). As can be discerned *vide infra*, this design feature was critical to enabling the remarkable level of generality observed for this deoxygenative coupling. Furthermore, we note that the benzoxazolium salt (**2**) is readily synthesized in two steps on 150 grams scale without any work-up or purification, and is now available commercially.

With an operationally simple protocol in hand, we first explored the scope of the deoxygenative arylation with respect to the alcohol component (Fig. 3). We were delighted to find that this activation mode was competent in delivering a diverse array of adducts arising from both stabilized and unstabilized radical species. For example, high-energy deuteromethyl and trifluoroethyl radicals were generated from deuteromethanol (**21**) and trifluoroethanol (**22**), respectively, to give arylated product in good yields. This technology is also compatible with alcohols bearing chiral *β*-substituents, including a free alcohol, amide, and enolizable ester, directly yielding chiral arylated products with 100% enantiospecificity (**23**–**25**). Importantly, a high degree of chemo- and regio-selectivity was observed in this reaction, as the NHC **2** preferentially activated the less-hindered primary alcohol in the presence of both a carbamate N–H bond (**24**) and a secondary benzylic alcohol (**25**).

We next examined a series of secondary alcohol coupling partners. As shown in Figure 3, a variety of cyclic alcohols, ranging in size from three- to seven-membered rings, underwent deoxygenative arylation in good to excellent yields. Viable motifs in this transformation include the cyclopropyl group (**33**), oxetane (**34**), azetidine (**35**), pyrrolidine (**37**, **38**), indane (**39**), menthol (**40**), piperidine (**41**), and diazacycloheptane (**44**). Alcohols located on pharmaceutically-relevant strained bridged bicycles, such as (**48**–**50**), gave arylated products with good diastereo-selectivity. Finally, acyclic secondary alcohols, such as **45** and the bulky pinacolyl alcohol (**46**), were successfully coupled. We note that this method has a reactivity profile orthogonal to common sp^2–sp^3 coupling protocols, as arylation occurs exclusively at the alcohol site (**42, 43**, **48**) while secondary alkyl bromides and carboxylic acid are left untouched.

We next probed whether tertiary alcohol substrates could be employed to generate quaternary carbon centers. We were pleased to find that, in the presence of a *N*-4-(trifluoromethyl)phenyl benzoxazolium salt activating agent, a variety of tertiary alcohols served as viable coupling partners in the deoxygenative arylation, see SFig. 7 for details. Thus, cyclopropyl (**51**), oxetane (**52**) and azetidine (**53**) tertiary alcohols gave the desired quaternary carbon product without any detectable regioisomers. An alcohol positioned at a [1.1.1]bicyclo bridge head (**54**) underwent homolysis to form a high-energy radical species en route to the desired arylation product. Moreover, arylation with the C2 tertiary radical of [1.1.1]bicyclopentane (**55**) was achieved for the first time. For more hindered and electron-rich tertiary radicals such as trialkyl acyclic (**56**–**57**), cyclic (**58**–**61**), or fused-ring bridgehead variant (**62**), we found that $Ni(TMHD)_2$ proved to be more effective to form the quaternary carbon centers. In contrast, $Ni(dtbbpy)Br_2$ catalyst gave only trace product with tertiary radicals, consistent with the reported ligand-induced change of mechanism for this C–C bond-forming step.[33]

Saccharides represent an important class of biological molecules, and the development of versatile methods by which to directly functionalize these alcohols is of particular interest. As shown in Figure 3, the hemiacetal at the anomeric carbon of commercially available pyranose (**66**) and furanoses (**63** and **64**) could be activated to provide the deoxygenatively coupled products with excellent diastereoselectivity. Similarly, chiral

alcohols on the ribose core (**65**) and hindered fructopyranose (**67**) were activated to generate the corresponding coupled products.

We next sought to evaluate the scope of the aryl halide coupling partner employing Boc-protected 3-hydroxy piperidine as the standard alcohol coupling partner. It is worth noting that this alcohol cannot be converted to the corresponding alkyl halide via a conventional Appel reaction.[34] As shown in Extended Data Figure 1, aryl bromides with different electronic properties (**68**, **69**) or bulky *ortho*-substituents (**74**, **75**) gave desired products in generally good yields. Importantly, many medicinally-relevant functional groups were well-tolerated, including: primary sulfonamide (**70**), aryl boronic pinacol ester (**71**), tertiary amine (**72**), primary benzyl amine (**73**), and free benzylic alcohols (**76**). We were pleased to observe that challenging five-membered heterocyclic bromides (**93**–**106**) generally participate effectively in this coupling. Moreover, we found that our standard conditions are also amenable to the coupling of electron-deficient aryl chlorides (**107**–**109**) and heteroaryl chlorides (**110**–**115**). Notably, the transformation can be used for the late-stage functionalization of the chloride-containing drug molecules Zomepirac (**108**) and Etoricoxib (**115**).

To further demonstrate the synthetic value of this new versatile technology, we sought to achieve sequential double-deoxygenative arylations of C2-symmetric diols (Fig. 4a). The condensation of NHC with 1,2-diol substrates was found to be highly mono-selective, ultimately yielding mono-arylated adduct (**121**–**123**) with high regio- and diastereoselectivity. These monoarylated products were then employed as starting materials en route to bis-arylated products, which were isolated with excellent diastereoselectivity in moderate to good yields (**126**–**128**). When commercially-available chiral diol **116** was employed, the enantiopurity was quantitively transferred to the bis-arylated product (**121**). Similarly, commercially-available C2-symmetric chiral 1,4-diols (**119** and **120**) were readily diversified into complex arylated products (**129**–**130**) with excellent diastereoselectivity. This chirality transfer technology is anticipated to provide a valuable new bond disconnection strategy for chiral pool synthesis.

We next sought to demonstrate the robustness of the coupling reaction in the context of complex, drug-like molecules (Fig. 4b). Toward this end, the blockbuster antidiabetic drug Januvia was synthesized in two steps from commercially-available starting materials. Under standard deoxygenative arylation conditions, the alcohol **132** was converted to enantiopure Januvia (**133**) in 65% yield. Four Januvia variants (**134**–**137**) were similarly prepared in straightforward fashion from intermediate **132**. To demonstrate the expansive utility of this cross-coupling strategy, we selectively functionalized the alcohol on the high-density core of the anticancer drug Taxol (**138**). Moreover, deoxygenative arylation of the lipid-lowering drug simvastatin proceeded in good yield (**139**).

To further demonstrate the generality of the aryl halide scope and its potential value in medicinal chemistry campaigns, we tested a Merck aryl-halide informer library, containing 18 different halides, using representative primary and secondary alcohols (Fig. 4c).[35] Of the 36 reactions performed, 28 gave synthetically useful yields for a medicinal chemistry program (0.1 mmol scale). With our protocol, an average yield of 50% was observed across the entire Merck halide informer library. This result represents the highest level of reaction efficiency to date for any sp^2–sp^3 coupling technology benchmarked by the informer library,[36] highlighting the power and versatility of this deoxygenative transformation for complex substrates.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-021-03920-6.

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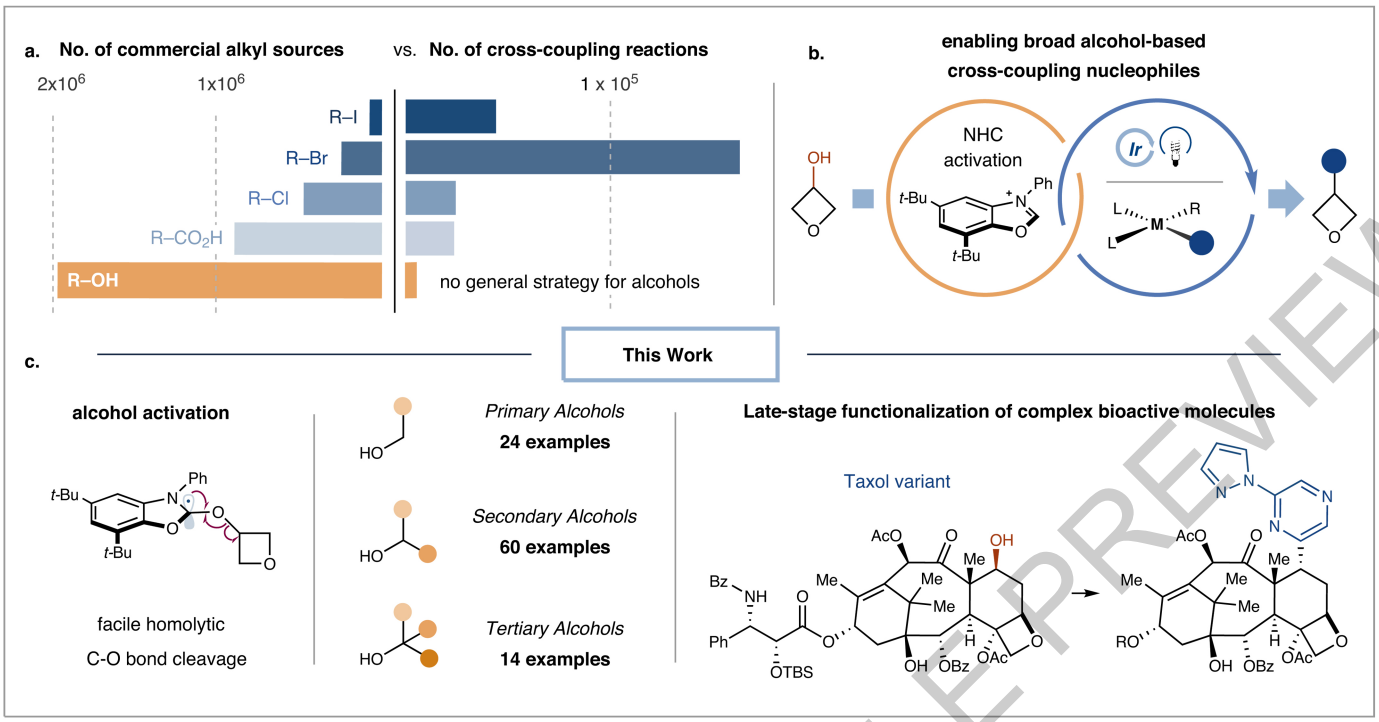

Figure 1 | Direct deoxygenative arylation of alcohols. a, Alcohols are the most widely available alkyl fragment; however, there is no general strategy for the use of alcohols as C(sp^3) fragments in cross-coupling reactions. **b**, A general strategy for the cross-coupling of alcohols is enabled by the merger of NHC-mediated alcohol activation, photoredox catalysis, and nickel catalysis. **c**, The success of alcohol deoxygenative cross-coupling relies on the facile NHC-mediated C–O bond homolytic cleavage. This method is amenable to a wide range of primary, secondary, and tertiary alcohols. This activation mode can be used for the late stage deoxygenative arylation of drugs, such as Taxol. NHC, nitrogen-heterocyclic carbene; Ac, acetyl; Bz, benzoyl; Me, methyl; Ph, phenyl; *t*-Bu, *tert*-butyl; TBS, *tert*-butyldimethylsilyl.

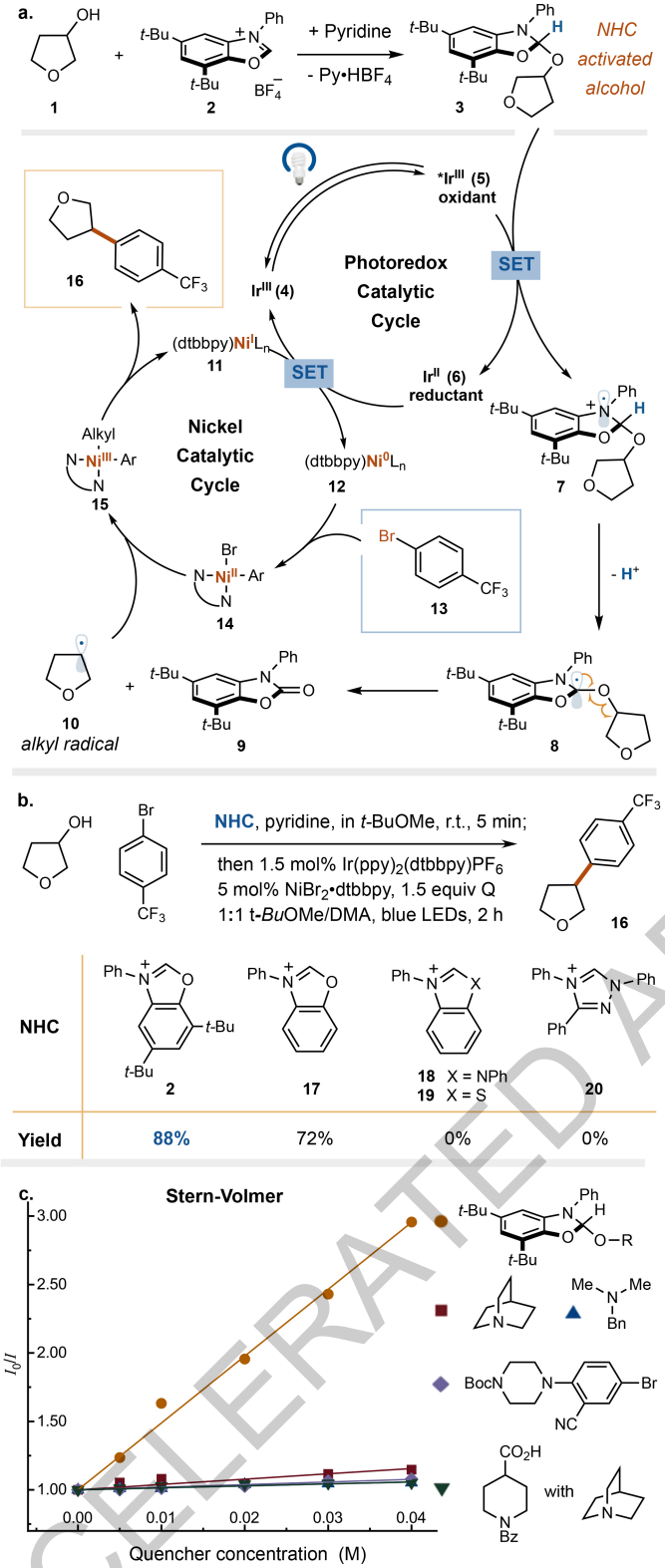

Figure 2 | Proposed mechanism and nitrogen-heterocyclic carbene evaluation for deoxygenative arylation. a, The starting alcohol **1** is converted to adduct **3** in the presence of NHC salt **2** and base. The deoxygenative radical **10** is generated from **3** upon sequential electron/proton transfer and followed by facile β-scission, which can be captured by Ni–aryl species **14** to yield the arylated product **16**. **b**, Evaluation of N-heterocyclic carbene salts for deoxygenative arylation. For detailed optimization, see Supplementary Information. **c**, Stern-Volmer quenching comparison of NHC-adduct **3** and other readily oxidizable functional groups. $Py.HBF_4$, Pyridinium tetrafluoroborate; Q, quinuclidine; *t*-BuOMe, methyl *tert*-butyl ether; DMA, dimethylacetamide; R, 3-tetrahydrofuranyl.

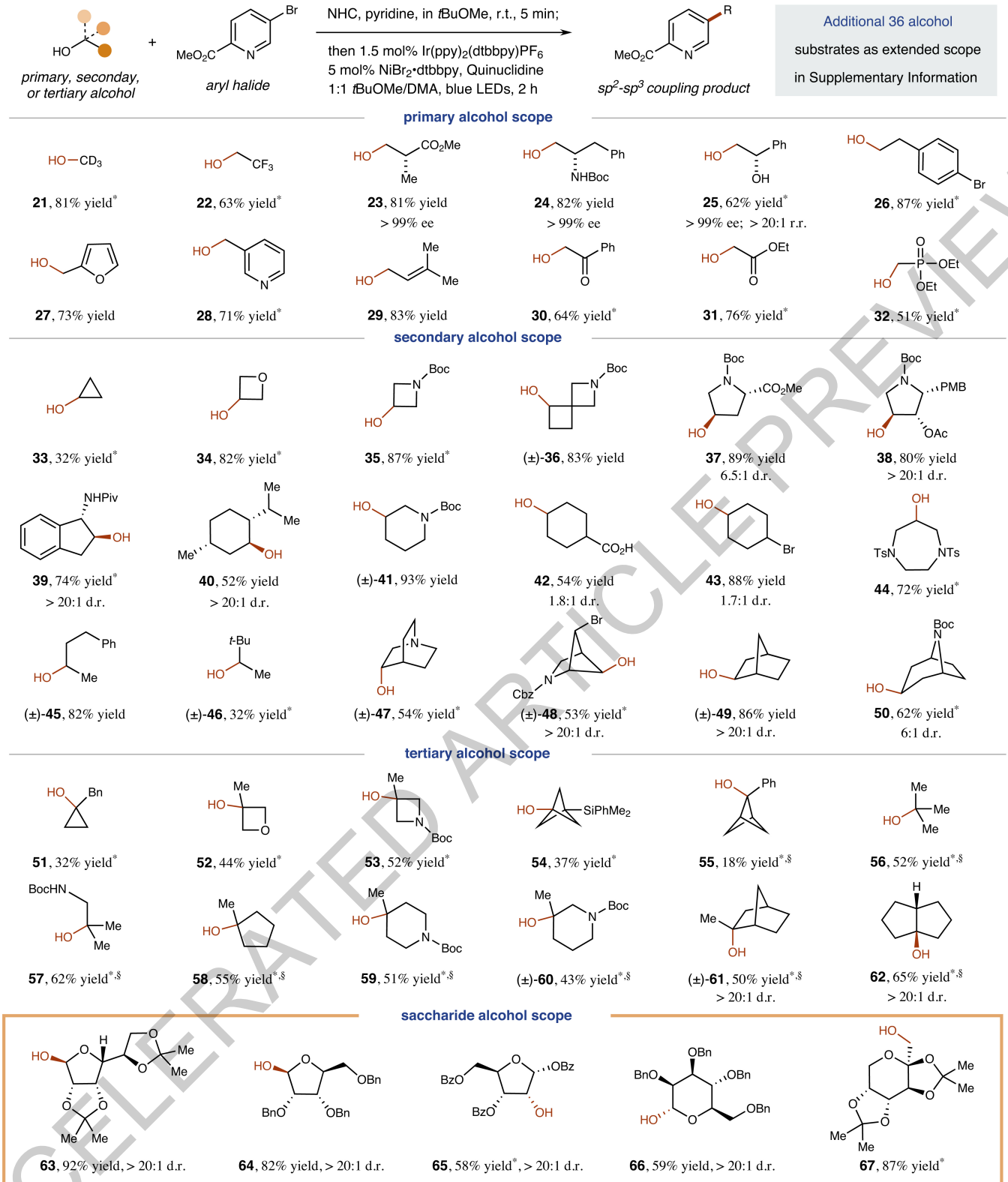

Figure 3 | Alcohol scope for deoxygenative arylation. Primary, secondary, and tertiary alcohols can be used as alkyl coupling partners in the arylation. All yields are isolated unless otherwise noted. Experiments typically run with 1.0 equiv. of aryl halide, 1.7 equiv. of alcohol and 1.6 equiv. of NHC salts on 0.5 mmol scale. *See Supplementary Information for experimental details. §$Ni(TMHD)_2$ and methyl 4-bromobenzoate are used as catalyst and aryl halide coupling partner respectively. Boc, *tert*-Butyloxycarbonyl; Bn, benzyl; Et, ethyl; PMB, 4-methoxybenzyl; Piv, pivaloyl; Ts, 4-toluenesulfonyl; $Ni(TMHD)_2$, Nickel(II) bis(2,2,6,6-tetramethyl-3,5-heptanedionate).

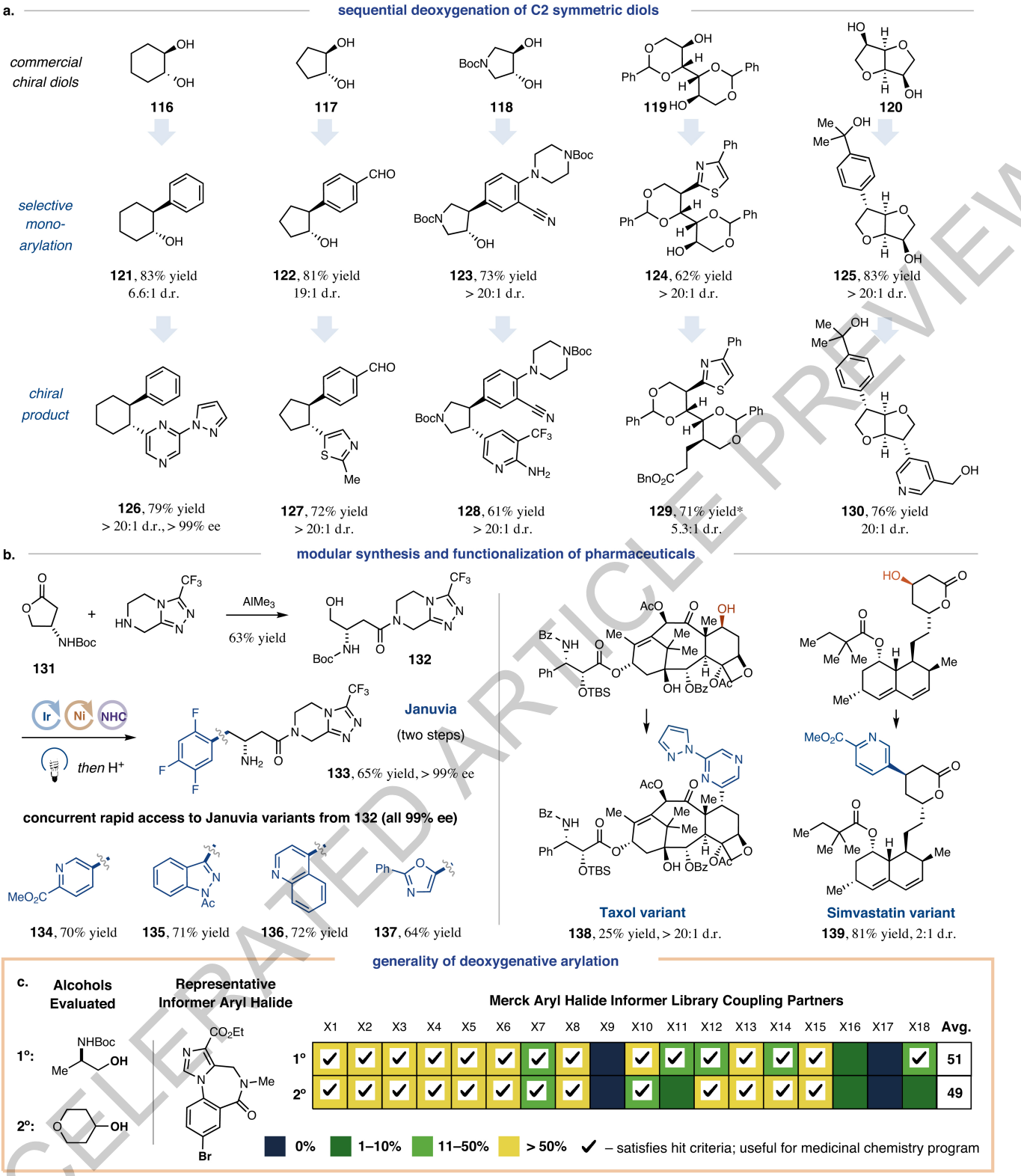

Figure 4 | Chirality transfer from chiral diol and late-stage drug molecule functionalization. a, Double deoxygenative functionalization of commercially available C2-symmetric diols permits transfer of chirality to bis-arylated products via diastereocontrol. *benzyl arylate was used instead of nickel catalyst. **b**, This protocol can also be applied to a modular synthesis of Januvia and its variants, as well as to the late-stage functionalization of pharmaceutical variants, such as Taxol and Simvastatin. All yields are isolated, see Supplementary Information for exact conditions. **c**, To demonstrate the generality of the deoxygenative arylation, primary and secondary alcohols were evaluated with 18 different complex halides. Among 36 distinct combinations of coupling partners, 32 reactions successfully gave the desired product. Yields were obtained by UPLC analysis, see Supplementary Information for details.

Data availability

The data supporting the findings of this study are available within the paper and its Supplementary Information.

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Author contributions Z.D. performed and analyzed the experiments. Z.D. and D.W.C.M. designed the experiments. Z.D. and D.W.C.M. prepared this manuscript.

Competing interests The authors declare no competing interests.

Additional information

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

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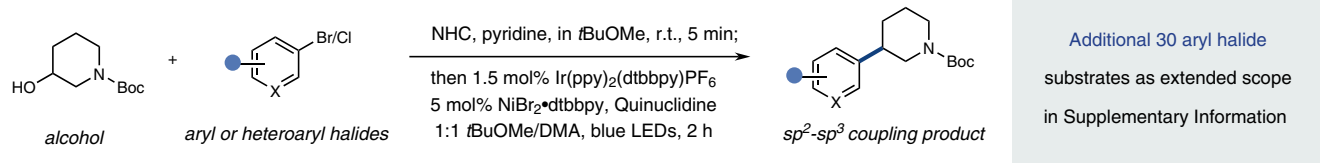
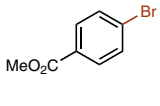
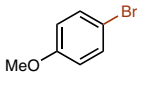


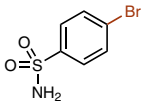
aryl bromide scope



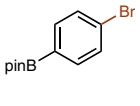
(±)-**68**, 86% yield



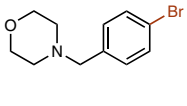
(±)-**69**, 81% yield



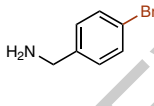
(±)-**70**, 76% yield



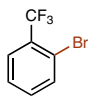
(±)-**71**, 82% yield



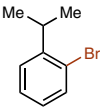
(±)-**72**, 86% yield



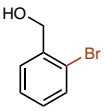
(±)-**73**, 48% yield



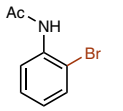
(±)-**74**, 71% yield*



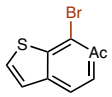
(±)-**75**, 56% yield*



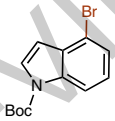
(±)-**76**, 72% yield



(±)-**77**, 79% yield



(±)-**78**, 78% yield

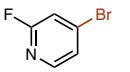


(±)-**79**, 81% yield

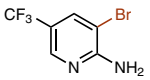
heteroaryl bromide scope

(±)-**80**, 68% yield*

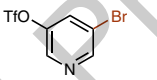
(±)-**81**, 89% yield



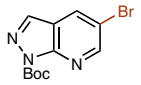
(±)-**82**, 81% yield



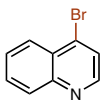
(±)-**83**, 72% yield



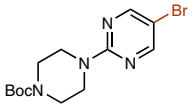
(±)-**84**, 83% yield*



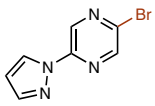
(±)-**85**, 81% yield*



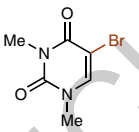
(±)-**86**, 90% yield



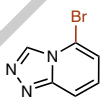
(±)-**87**, 76% yield



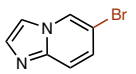
(±)-**88**, 78% yield



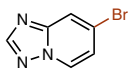
(±)-**89**, 63% yield*



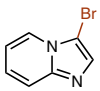
(±)-**90**, 60% yield*



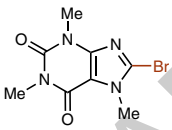
(±)-**91**, 55% yield*



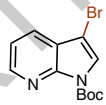
(±)-**92**, 64% yield*



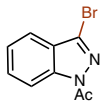
(±)-**93**, 51% yield*



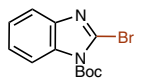
(±)-**94**, 75% yield



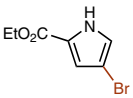
(±)-**95**, 65% yield*



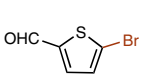
(±)-**96**, 84% yield



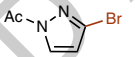
(±)-**97**, 82% yield



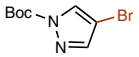
(±)-**98**, 54% yield*



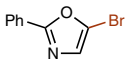
(±)-**99**, 73% yield*



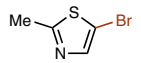
(±)-**100**, 76% yield*



(±)-**101**, 51% yield*

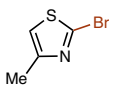


(±)-**102**, 82% yield*

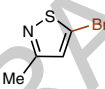


(±)-**103**, 86% yield*

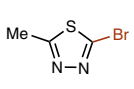
aryl chloride scope



(±)-**104**, 76% yield*



(±)-**105**, 82% yield*



(±)-**106**, 66% yield*

(±)-**107**, 76% yield

(±)-**108**, 62% yield

(±)-**109**, 63% yield

heteroaryl chloride scope

(±)-**110**, 92% yield

(±)-**111**, 63% yield*

(±)-**112**, 91% yield

(±)-**113**, 52% yield*

(±)-**114**, 61% yield*

(±)-**115**, 78% yield

Extended Data Figure 1 | Aryl halide scope for deoxygenative arylation. Both (hetero)aryl bromides and chlorides can be utilized under same reaction conditions. All yields are isolated. Experiments typically run with 1.0 equiv. of aryl halide, 1.7 equiv. of alcohol and 1.6 equiv. of NHC on 0.5 mmol scale. *See Supplementary Information for experimental details.