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Accessing aliphatic alcohols for metallaphotoredox catalyzed C(sp^3)-arylation

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Common cross-coupling reactions to obtain C(sp^2)–C(sp^3)-bonds are hampered by the abundance of nucleophilic and electrophilic functional groups. Recently in *Nature*, Dong and MacMillan developed a mild activation of a diverse range of alcohols with an N-heterocyclic carbene (NHC) salt and merged it with nickel photoredox dual catalytic arylation.

The development of methodologies for C(sp^3)–C(sp^3) coupling reactions allows access to a multitude of molecules because this bond is ubiquitous in organic chemistry, ranging from materials science to medicinal chemistry. Early examples relied heavily on the use of organometallic reagents, such as Grignard reagents, organozincates, or boronates, mechanistically following the inventions of powerful palladium-catalyzed cross-coupling reactions. Without a doubt these findings represent powerful transformations that forge the desired C(sp^3)–C(sp^3) bonds by coupling with aryl halides. However, in many cases organometallic reagents are synthesized from the respective alkyl halides, which in return offer more widespread commercial availability compared to their metallic counterparts (Figure 1A). Reductive coupling—in particular, between aryl bromides and alkyl bromides—was pioneered by the Weix group in 2012, who found that nickel catalysis is particularly powerful in this transformation. A key feature of these nickel catalysts is easy access to a variety of oxidation states that can interact with transient radicals formed during the reaction. Additionally, nickel is less prone to β-hydride elimination. Utilizing alkyl bromides was found to give improved conversion within the halide scope, since alkyl iodides are easier to activate (bond dissociation energy (BDE) = 55 kcal/mol) but are prone to reduction and dimerization side products. C(sp^3)–Cl bonds, on the other hand, are more difficult to break than those of alkyl bromides (BDE = 86 instead of 70 kcal/mol) and therefore show significantly lower reactivity, which rendered aliphatic bromides the perfect substrate to investigate C(sp^3)–C(sp^3) coupling reactions. In follow-up investigations, the use of stoichiometric reductants like zinc or manganese hampered homogeneity of the reactions. A mild visible light-driven arylation approach was pioneered by the MacMillan group in 2014, when aliphatic carboxylic acids were employed in this metallaphotoredox catalytic protocol. The carboxylic anion was oxidized by an excited state iridium(III) photocatalyst to yield a C(sp^3)–centered radical, which underwent bond formation with aryl bromides upon nickel catalysis. This protocol renders decarboxylation a powerful tool by using abundant native functional groups (see Figure 1A) and enabling arylation reactions for drug derivatization.

However, activating aliphatic alcohols as functional groups, which are widely available in nature, remains rather underdeveloped in cross-coupling, in a sharp contrast to those radical hydrodeoxygenations following Barton and McCombie’s original report. Catalytic arylations of benzyl or allylic alcohols were described consecutively in 2018, requiring titanium or zirconium as deoxygenating agents and stoichiometric manganese as reductant. In 2021, the Li group investigated the electrochemical arylation of aliphatic alcohols to obtain a wide range of C(sp^3)–C(sp^3) coupled products. Their protocol relied on the in situ Appel reaction with up to seven equivalents of triphenylphosphine and lithium bromide to form the respective alkyl bromides, which didn’t solve the homolytic cleavage of the strong C–O bond.

In order to establish a broadly applicable alcohol cross-coupling technique (1) C(sp^3)-OH cleavage should be feasible, despite the large BDE (between 92-95 kcal/mol); (2) no additional chemical steps or purifications should be included; (3) the full scope of alcohol classes should be accessible; (4) the involved reactive intermediates should be amenable to transition-metal catalysis; and (5) to get real world application, the presence of other functional groups should not interfere in the reaction. This combination already sets quite a high bar to achieve for a single cross-coupling strategy but nevertheless would allow entry to the full scope of primary, secondary, or tertiary aliphatic alcohols prevalent in nature (Figure 1A).

Starting off from these requirements, Dong and MacMillan found that electron-deficient N-heterocyclic carbene (NHC) salts, namely benzoazolium salts, can condense readily with aliphatic alcohols in the presence of weak bases like pyridine (Figure 1B). These adducts commonly suffer from reversibility of the condensation step, which would release an NHC capable of coordinating to the metal catalyst in the reaction. With this in mind, electron-deficient NHCs were found to form alcohol adducts irreversibly for efficient alcohol activation in order to enter an open-shell mechanism, compared to traditional ones like benzimidazolium or benzothiazolium salts.

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The condensation step is high yielding, fast (< 5 min), and irreversible, as no exchange with other alcohols was observed after successful adduct formation.

The benzoxazol adducts, which are obtained from ethereal solutions, can be used directly in the cross-coupling reaction without further treatment and undergo oxidation by excited-state reductive quenching of an iridium photocatalyst (Ir(ppy)2(dtbbpy)PF6), as identified by Stern-Volmer quenching experiments with different possible functionalities. Upon facile deprotonation.

Figure 1. NHC-mediated deoxygenation of aliphatic alcohols enabled metallaphotoredox-catalyzed arylation reactions

(A) Aliphatic alcohols are by far the most accessible functional groups based on their relative commercial availability (scifinder.cas.org, 13-08-2021) and prevalence in nature.

(B) Dong and MacMillan developed a condensation strategy with alcohols and NHC’s to enable deoxygenative metallaphotoredox C(sp2)–C(sp3) cross-coupling.

(C) The protocol is amenable to a vast range of all classes of alcohols, can tolerate various (hetero)aryl halides, and enables the editing of drug molecules.
with quinuclidine as base, a carbon-centered C(sp³) radical is formed in the benzoxazoline ring with three adjacent heteroatoms. This unique radical intermediate A undergoes β-scission and releases the aliphatic residue as a deoxygenated C(sp³) radical from the alcohol as a formal homolytic C–O bond cleavage, meanwhile forming the rearromatized benzoxazoline (Figure 1B). This aromatization energy is expected to be the thermodynamic driving force of this reaction. The so-formed C(sp³) radical can subsequently be trapped by a Ni(II) catalyst, in situ formed by oxidative addition of an aryl halide. Reductive elimination from the Ni(III) catalyst yields the final C(sp²)–aryl halide. Reductive elimination from the Ni(III) catalyst yields the final C(sp²)–aryl halide, preferentially bromides or chlorides, and yields high conversions for five- or six-membered rings, respectively. Since halide-containing drug molecules like Zomepirac or Etoricoxib can be derivatized with aliphatic alcohols, the protocol was tested against Merck’s aryl halide inhibitor library and revealed a remarkable performance across 28 (out of 36) different substrates with an average yield of 50%.

With this tool in hand, up to 86 aliphatic mono-alcohols and five different diols can replace all kinds of electrophilic or nucleophilic functional groups in cross-coupling reactions, which otherwise need to be prepared, often starting from alcohols. The scope gives also access to alcohols, which cannot be transferred into the respective electrophiles by SN₂ reactions. The deoxygenation tolerated up to 78 different aryl halides featuring multiple functional groups like benzylalcohols and tertiary amines, boronic esters, or carbonyl groups. Applicability in editing alcohol- or halide-containing drugs was demonstrated, enabling late-stage functionalization of potent drug candidates. It is expected that this protocol drastically changes the design of organic molecules, thus opening an enormous chemical space in conjunction with a mild and operationally simple procedure.

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